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SYMPOSIUM

Management of Patients With Primary (Essential) Hypertension

INTRODUCTION

THE physician, confronted with the dilemma of choosing the optimal treatment for the various phases of primary (essential) hypertension, often wishes guidance from the expert in the field. This issue of the JOURNAL has been prepared to assist in this need.

The views of an able group of hyperpiesiologists have been obtained. Their opinions are presented according to the following plan. The lead article by Dr. Perera points out those periods in the life of the individual with hypertension in which the family physician is called upon to make important therapeutic decisions. Dr. Perera then defines the criteria which must be met in appraising the value of various forms of treatment. In so far as it was possible, each of the other participants in this "literary consultation" (Drs. Grob, McMichael and Murphy, Page, Schroeder, Smirk and McQueen, Smithwick, Wertheim and Deming, and Wilkins) has directed his recommendations against the background of the lead article.

In reviewing these reports, the internist or surgeon (and other interested members of the paramedical disciplines) can have the counsel of experts in the field whose combined experience in the management of hypertension is unmatched. In effect the physician has access to a helpful office or bedside consultation. As the family physician, he alone can decide which of the various opinions he wishes to follow in the case of a particular patient.

DAVID SEEGAL

HYPERTENSIVE VASCULAR DISEASE: THERAPEUTIC PRINCIPLES AND OBJECTIVES

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VOL.
1
195

"YES, I know all that," commented a member of the medical audience during the question-and-answer period which followed a discussion of the principles governing the treatment of hypertensive vascular disease. "But I see patient after patient with high blood pressure, and each one wants something done about it. What do you *do* for hypertension?"

A fair question! It has become apparent that there is a place at times for diet, drugs, and surgery, a place in some instances for an experimental trial or a placebo, and, of course, there is always a place for reassurance and the relief of anxiety. There is sometimes a place to do nothing; this can be accomplished only if the physician enjoys the patient's confidence and is prepared to take time and trouble. It is clear that whatever therapeutic program is decided upon, it will assume greater meaning if there is a clear understanding of the evolution of the disease and of the objectives to be achieved.

Proper evaluation of a proposed therapeutic regimen must be based first on comparison with the natural history of the untreated disorder. To recapitulate briefly,[1] hypertensive vascular disease (primary or essential hypertension) has an average duration of close to twenty years from the inception of an elevated blood pressure until death. On the average, fifteen of these years are spent in an *uncomplicated hypertensive phase*, sometimes without symptoms, more often with intermittent complaints such as nervousness, dizziness, headache, and palpitation. Thereafter comes a period of *complications*, arising from variable degrees of cardiac hypertrophy, arterio-, and arteriolosclerosis, and leading to death in approximately five years. A small percentage of patients, either from the outset or at any time in the course of their hypertensive disease, develop an *accelerated* ("*malignant*") *phase*, which is fatal as a rule within one or two years. These are average data; the individual variability is great.

Some of the complications of hypertensive vascular disease are episodic events which at the present time are managed in much the same manner as in normotensive patients. Cerebral vascular accidents, angina pectoris, and cardiac infarction—resulting from atherosclerotic changes—are in this category, as is uremia, encountered in advanced nephrosclerosis or in the terminal stage of the accelerated phase. Their presence may modify or even contraindicate

certain forms of therapy, such as the more powerful hypotensive drugs or sympathectomy. Congestive failure, on the other hand, is either secondary to atherosclerosis or may be produced in part by fibrotic damage in a hypertrophied heart; that form not directly due to organic coronary artery disease is often amenable to specific hypotensive measures. Retinopathy and nephrosclerosis may appear during the phase of complications as manifestations of arteriolosclerosis.

The clinical diagnosis of the accelerated phase,* as defined in this clinic, requires the presence of progressive renal damage. During this phase, retinopathy and papilledema are common, and infrequent encephalopathic crises† may occur. Retinal or renal changes may be part of the period of complications or the accelerated phase; it is the rapid velocity, the finding of papilledema if present, and the ultimate pathologic picture which characterize the accelerated phase and separate it from the type of arteriolosclerotic complications described previously.

From these considerations, discussions of treatment of hypertensive vascular disease may be usefully presented under the following major subdivisions:

1. Uncomplicated phase
   a. Asymptomatic
   b. Symptomatic
2. Complications
   a. Cardiovascular
   b. Arteriolosclerotic
3. Accelerated phase
   a. Encephalopathy
   b. Without nitrogen retention
   c. With nitrogen retention

It is obviously important, if comparative evaluations are to be meaningful, that definitions, terminology, and classification be made as uniform and accurate as possible.

"What do you do?" The answer to this question assumes greater meaning if there is prior consideration of "What are you trying to do?"

What are the objectives sought in the treatment of hypertensive vascular disease? Ideally, they would be to find the cause and remove it. This is not yet possible. Next best would be to determine the mechanisms responsible for

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*Characterized by an accelerated velocity, progressive emphasis on and damage to the renal area, and death in uremia unless the course is terminated along the way by coexistent brain or heart damage. Pathologic examination reveals that the majority have developed a necrotizing arteriolitis. A few will show only extensive arteriolar alterations in the kidneys. The term "accelerated phase" is employed as a clinical description, and the expression "accelerated phase with necrotizing arteriolitis" reserved for those in whom there is pathologic confirmation.[1]

†Acute cerebral manifestations, characterized by headache, vomiting, convulsions, and even coma associated with a rapid rise in blood pressure, and not accompanied or followed by sensory or motor signs.[1]

the greater incidence of cardiac hypertrophy, arterio-, and arteriolosclerosis in hypertensive individuals. If one could prevent the development of these pathologic changes, even hypertensive patients might live to a normal life expectancy. In the absence of such specific controlling measures there would remain these justifiable objectives: To educate the patient to live with his disease, to relieve apprehension and fear, to deal with bothersome and sometimes incapacitating symptoms, and, if one cannot give added "years to life," then to give "life to years."

The following broad generalizations have a particular bearing on the management of hypertensive vascular disease: (1) It is evident that the beneficial value of any potentially therapeutic measure, whether it be diet, drug, or surgery, must be weighed against the possible invalidism, restricted life, side effects, and toxicity induced by that measure. Even reassurance may present a calculated risk. I recently supported the wish of a hypertensive woman without complications to get married; she sustained a cerebral hemorrhage on her wedding night. (2) Beneficial therapeutic results achieved in patients in one hypertensive phase should not be translated to other phases until it is established that they can be produced in these other phases. (3) The possible adverse effect of a hypotensive measure on the blood flow to some local circulatory area must be kept in mind, especially in a disease giving rise to degrees of cerebral, coronary, or renal blood vessel damage which are often undetectable. (4) Many of the therapeutic measures currently employed produce dissimilar magnitudes of response and degrees of tolerance when applied to different individuals. Hence evaluations of therapy must be based on sound statistical evidence, and the treatment of each individual patient must be looked upon as an experiment or as part of a group study.

There is now fairly general agreement that means are available in many hypertensive patients (1) to relieve symptoms beyond the point achieved by time, rest, prolonged hospital care, or psychotherapy, (2) to lower the blood pressure to almost any desired level, (3) to modify some complications of the disorder, such as congestive failure and retinopathy, and (4) to prolong the life of some individuals in the accelerated phase. The results so obtained must be balanced by the relative risks of the methods employed. At any rate, there is considerably less agreement when one attempts to add further to this list of achievements. For example, there is no convincing proof as yet that any therapeutic measure has lengthened the life of a hypertensive individual in the uncomplicated phase.

Is the level of the blood pressure a major factor in the development of the complicating pathologic changes? Elevation of the arterial tension should increase the work of the heart and hence should favor its hypertrophy. High pressure is an admitted factor in the production of certain forms of experimental atherosclerosis. Furthermore, favorable responses to therapy are encountered most commonly after the application of hypotensive measures. These facts suggest but do not establish an affirmative answer to the propounded question. Contrary evidence is based on the observations that clinical progression sometimes fails

to develop despite unusually high and long-sustained blood pressure levels, that there is a lack of correlation between the effect of sympathectomy on blood pressure and on other manifestations of hypertensive disease, and that definite progression of certain pathologic changes occurs on occasion even after the blood pressure has been lowered. These facts suggest but do not establish a negative answer to the question. One must await longer studies and more knowledge of diurnal fluctuations of blood pressure levels. At any rate, it may be argued that the direction of therapeutic emphasis might be radically different provided the question had an unequivocal answer.

If the blood pressure is related to pathologic alterations, are the peaks of elevation more harmful than the basal or resting levels? This question can be answered only if the previous question is found to have a solution in the affirmative. Sympathectomy and many drugs prevent overshoots of the arterial tension, but basal levels may also be modified, especially in conjunction with orthostasis. Clinical improvement might be related to one or the other of these effects or might, as suggested previously, be quite independent of the induced blood pressure changes. Again there is need for more information before a definitive statement can be made.

Does the accelerated phase represent only a quantitative increase in the tempo of the disease? It is usual for levels of blood pressure to be higher in the accelerated phase, and procedures which lower the blood pressure are associated generally with regression of some of its manifestations. On frequent occasions, however, renal dysfunction fails to be relieved by reduction of blood pressure. On rare occasions, there may even be progression of retinal lesions despite marked reductions of blood pressure.[2] The accelerated phase sometimes begins de novo (without antecedent hypertension) and has a different sex incidence from other phases of hypertensive vascular disease.[1] Its relation to primary renal disease, particularly to unilateral renal disease, demands some other explanation. Perhaps, after hypertensive mechanisms have given rise to an extensive or appropriate type of renal injury, the kidneys themselves become responsible for the pathologic features of the accelerated phase. Serious consideration must be given to possible causative factors other than those related only to the degree of arteriolar vasoconstriction.

Are the mechanisms which produce retinopathy identical with those which produce nephrosclerosis and renal damage? If the lives of some patients in the accelerated phase are prolonged by therapy, is one justified in assuming that a reversal of the pathologic process has occurred? Treatment during the accelerated phase may reverse the retinal lesions and, especially when instituted before the development of much nitrogen retention, probably prolongs life to some extent. This does not prove that the primary disease has been altered, for a longer survival might be the result of influences exerted on secondary factors, for example, improvement in congestive failure. Therapy is less effective in the presence of advanced kidney damage, and in some situations retinopathy has vanished in association with hypotensive measures although extensive necrotizing arteriolitis is demonstrated at necropsy.

These are not irrelevant questions. Their ultimate answer may throw important light on some of the mechanisms of the hypertensive process. Of greater concern is the fact that, until they are answered, one is not justified in using the hypotensive response as the sole criterion of improvement in hypertensive vascular disease and in regarding minor shifts in average survival figures as proof of modification of the whole disease process. Unless these questions can be answered in the affirmative, which I regard unlikely, final evaluation of therapeutic results must be interpreted with extreme caution.

"Yes, I know all that—but what do you *do* for hypertension?"

Discussion of "What do you do for hypertension" will follow. It is to be hoped that the physician, as he considers the problems presented by each of his patients, will also see the reason for asking: Why? How? What is the evidence? Is it worth the effort? Is it safe? What am I really doing?

VOL
1
195

REFERENCES

1. Perera, G. A.: Hypertensive Vascular Disease; Description and Natural History, J. CHRON. DIS. **1**:33, 1955.
2. Perera, G. A.: Development of Hypertensive Manifestations After the Disappearance of Hypertension, Circulation **10**:1, 28-29, 1954.

HYPERTENSIVE VASCULAR DISEASE

Results of and Indications for Splanchnicectomy

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OL.
1
955

INTRODUCTION

THIS report is intended to be a brief summary of what my associates and I have been doing for hypertension for the past twenty years. In response to Dr. Perera's[1] question—What do you do for hypertension?—I will attempt to describe what we have done and what we believe we have accomplished; since this forms the basis for what we recommend and do for hypertension.

Since 1925, I have been interested in the surgical approach to cardiovascular diseases in general. Surgical procedures may be divided into two categories, direct and indirect. An operation which deals with the lesion itself is a direct approach. So far as this particular problem is concerned, the excision of a segment of the aorta as for coarctation and the removal of a pheochromocytoma are examples of the direct surgical approach. There is no direct surgical approach to the causative mechanism in the vast majority of patients with hypertensive vascular disease. Consequently, an indirect approach by way of the sympathetic nervous system, which is known to exert an important influence upon the tone and reactivity of the smooth muscle of the arterioles, has been utilized. Surgical interest in the possibility of modifying the course of hypertensive vascular disease by removing the sympathetic innervation of large portions of the vascular bed received its most important stimulus from the preliminary report of Peet,[2] who described his early experiences with resecting the splanchnic nerves above the diaphragm, bilaterally, in a small series of patients with severe forms of hypertensive disease. The early results were encouraging, and this general approach to the problem seemed as logical as any therapeutic measure could be, granting the fact that the cause of the disorder was unknown. There are many diseases or disorders for which nonspecific therapy of one sort or another is well worth while, notably, cancer. To withhold treatment because the cause of a disease is unknown would be a mistake, although admittedly it is more logical and satisfactory when treatment is based upon a thorough understanding of etiological mechanisms. All therapeutic measures which are available today for the vast majority of patients suffering from hypertensive vascular disease are nonspecific in nature. This is true whether one employs psychotherapy,

diets, drugs, or an indirect surgical approach, such as splanchnicectomy. It is well to keep this in mind since at times doctors may become unduly enthusiastic about the results of nonspecific therapy for disease processes, to the point where they think a particular problem is really solved. It is most unlikely, in my opinion, that this problem will ever have an entirely satisfactory solution until therapy is based upon a sound knowledge of causative mechanisms and until we have the ability to appraise them in the individual patient.

The first problem to be solved so far as this indirect surgical approach is concerned was what portion of the sympathetic nervous system should be removed, how extensive the operation should be, and what was the best way to deal with this portion of the anatomy from the technical viewpoint. There are two ways of evaluating different types of sympathectomy. One is to attempt to select series of patients as nearly identical as possible, utilize a different operation in each, and at the end of a suitable period of time, compare the results. This is a satisfactory method to employ if one is dealing with a disease process which is reasonably comparable from patient to patient. Such, unfortunately, is not the case with the disorder under discussion. There are so many variables which should be taken into consideration from patient to patient that it would require different series of patients, each of large size, to hope to determine the relative merits of different operations. The same would apply to the evaluation of various diets or drugs.

A second method of appraising different types of sympathectomy is to select a carefully studied series of patients and to evaluate the efficacy of different types of sympathectomy in the same patients. This was the method which we adopted, since it seemed probable that some conclusion could be reached in a reasonable period of time utilizing a comparatively small series of patients. It took five years to complete this study. Multiple-stage operations were performed in each patient starting with a minimal procedure and adding to it until certain physiologic effects were noted as to both blood pressure levels and responses. It was soon apparent that certain operations were inadequate and others were too extensive. By the end of 1938, the conclusion was reached that for most patients, a so-called lumbodorsal splanchnicectomy appeared to be the operation of choice. It was best performed through an extrapleural retroperitoneal approach, dividing the diaphragm so as to give ready access to the portion of the sympathetic nervous system to be removed and to the kidney and adrenal glands as well. We were cognizant of the fact that renal disease might be an important etiological factor on the basis of the writings of Bright,[3,4] Gull and Sutton,[5] Moritz and Oldt,[6] Goldblatt,[7] and Page,[8] as well as many others. We also became aware of the physiologic implications in the writings of Homer Smith and his associates.[9] We realized that pheochromocytomas and paragangliomas were occasionally the cause of hypertensive vascular disease and wished to be certain that tumors of this sort were not overlooked. This approach also enabled us to inspect the kidneys and main renal arteries at the time of operation. As a result, a number of examples of hypertensive disease due to unilateral renal disease have been detected. Also, many pheochromocytomas have been found. Renal biopsies have been taken from kidneys in over

VOL. 1 1955

2,500 patients in various stages of the disorder. Renal blood flow studies have been correlated with the renal biopsy findings.[10] The results have convinced us, at any rate, that renal arteriolar disease is not the primary event in the development of the great majority of cases of hypertensive vascular disease.[11-14] Our conclusions in this respect are quite comparable to those of Gull and Sutton and in contrast to those of Bright, Moritz and Oldt, and Goldblatt. Furthermore, our findings tend to cast doubt that a physiologic aberration of renal blood flow, as evidenced by constriction of the efferent glomerular arterioles, is the primary event, since this abnormality does not appear to take place in most instances until a significant degree of renal arteriolar sclerosis, as judged microscopically, has already developed.

TABLE I. SPLANCHNICECTOMY FOR HYPERTENSION: OPERATIVE MORTALITY

GROUP*	NO. OF CASES	NO. OF DEATHS	MORTALITY (%)
1	299	2	0.7
2	1,399	20	1.4
3	486	21	4.3
4	219	24	10.9
Total	2,403	67	2.8

*Classification of groups as described in Tables II and III.

In our study of the extent of sympathectomy, we came to the conclusion that if carried beyond a certain point, the untoward physiologic effects detracted from the favorable effects. Total sympathectomy was found to be impracticable and more than a human being should be asked to tolerate. Lumbodorsal splanchnicectomy of a certain extent, namely, the removal of both sympathetic trunks and the splanchnic nerves arising from them, from the eighth thoracic through the first lumbar ganglia, inclusive, was the procedure which gave the best results with a minimum of untoward physiologic effects in the great majority of patients. It was well tolerated and could be carried out with a low operative mortality except in the most advanced cases (Table I). We found, however, that it should not be performed in two types of patients, namely, those with excessive tachycardia and those with coronary heart disease with a clear-cut history of angina pectoris. In these patients who represent about 10 per cent of those undergoing splanchnicectomy, a transthoracic sympathectomy and splanchnicectomy removing the sympathetic trunks bilaterally from the inferior cervical or second thoracic through the twelfth thoracic ganglia, inclusive, should be performed instead. The more extensive procedure is used in the angina and the less extensive in the tachycardia group. This matter has been discussed in detail elsewhere.[15,16] In the early years, the procedure of lumbodorsal splanchnicectomy was carried out in two stages about ten days apart. The hospital stay averaged twenty-eight days. In recent years, it has been performed in one stage. The hospital stay averages eighteen days and the patients are able to begin to resume their occupations two months after operation. The morbidity and mortality

of operation have not increased since the one-stage procedure was adopted. The results of operation, which will be discussed presently, are for the lumbodorsal maneuver, since the vast majority of patients were treated in this fashion. This operation was first described in 1940.[17]

CLINICAL INVESTIGATION OF LUMBODORSAL SPLANCHNICECTOMY AS A TREATMENT FOR HYPERTENSIVE VASCULAR DISEASE

The clinical investigation of lumbodorsal splanchnicectomy as a treatment of hypertensive vascular disease, the results of which form the basis for this

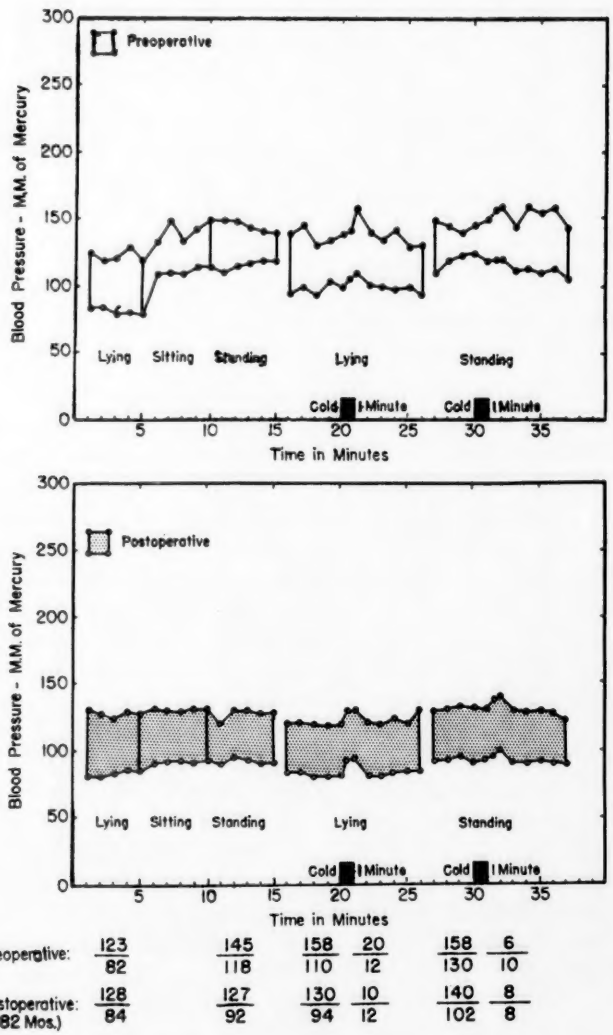

Fig. 1. *(For legend see opposite page.)*

VOL. 1 1955

report, was begun toward the end of 1938, about sixteen years ago. It is not completed as yet, which gives one some idea of how long it takes to evaluate any form of therapy for this disorder. Having decided upon the technique of operation, we next agreed upon a plan of study for each patient so that the same information obtained in the same manner would be available in each case. That was deemed essential since there are so many variables to be taken into consideration. This is particularly true as regards blood pressure data. We decided to utilize trained technicians and to secure blood pressure data by means of the postural and cold blood pressure test (Fig. 1) in each case. In addition, four hourly blood pressure readings were obtained as a routine. Technicians were employed because they obtained lower readings than physicians. The blood pressure data were obtained after forty-eight hours of hospitalization since these readings were invariably lower than ambulatory office or clinic readings. We did not wish to think we were dealing with patients with transient or so-called intermittent hypertension, by which we mean individuals whose blood pressure levels are only intermittently elevated. Such patients, even though ambulatory levels may always be abnormally high, will have readings within the normal range after a short period of rest (Fig. 1). This represents an earlier stage of the disease and carries a much better prognosis. One should know whether the blood pressure of a patient will readily fall to normal spontaneously before attempting to evaluate hypotensive therapy. Ambulatory base-line readings

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Fig. 1.—Blood pressure levels before operation (resting) and seven years after operation (ambulatory) are compared by means of the postural and cold blood pressure test. Readings are taken every minute for five minutes with the patient lying, then sitting, then standing. A cold test is then performed first when the patient is lying and is then repeated in the upright position. In these tests, five readings of blood pressure at one-minute intervals precede and follow one minute of immersion of one hand in ice water. Preoperatively, the resting blood pressure readings in the horizontal position averaged 123/82, in spite of the fact that ambulatory readings had averaged 180/120 for one year prior to operation. The readings in the upright position before operation averaged 145/118. The reflex rise in blood pressure of 22/36 mm. incident to assuming the upright position is very abnormal. The normal reflex response to the upright position is 4/12 mm. Many hypertensive patients have an abnormal postural response. It is always abolished by splanchnicectomy. The highest blood pressure reading (158/130) was in response to stimulation by cold in the upright position, although the magnitude of the cold response itself (6/10 mm.) was not abnormal (more than 20/15 mm.). It nevertheless represents the summation of the effects of two stimuli. Postoperatively all readings and responses were normal. It should be emphasized that the patient had intermittent, not continued, hypertension. The patients discussed in this report all had continued hypertension with this single exception. This case is used to illustrate an exception to the rule that the vast majority of patients with intermittent hypertension do not have cardiovascular disease. The vast majority of patients with continued hypertension do have cardiovascular disease. The presence of cardiovascular disease of consequence is a clear indication for instituting therapy.

Prior to operation this 40-year-old South African physician had Grade 4 eyeground changes with extensive hemorrhages and exudate, a normal-sized heart, an abnormal electrocardiogram, and normal renal function as judged by urinalysis, a urine concentration test, an intravenous P.S.P. test, and an intravenous pyelogram. Renal biopsies revealed Grade 3 arteriolar sclerosis (the most advanced is Grade 4). Seven years after operation the cardiovascular findings were normal in every respect, including the blood pressure levels. The latest report, eleven years after operation, reveals the situation to be the same. The blood pressure levels (ambulatory) at that time were lying 115/75, standing 118/83, maximal response to cold lying 120/80, standing 123/83.

This must be regarded as a satisfactory result. The patient has had no restrictions as to diet. He has had no medication. He has led an active life. Since we have followed many hundreds of patients with continued hypertension with equally or more severe cardiovascular changes for comparable periods of time with similar results, following splanchnicectomy alone or if necessary combined with a medical regimen consisting of a reasonable restriction of sodium intake and, if indicated, the use of one of the less toxic drugs, the question might be raised as to whether a more drastic medical regimen alone, if equally effective, could be considered to be an equally satisfactory way to manage patients with the more severe forms of hypertensive vascular disease for long periods of time.

are not satisfactory. The period of forty-eight hours' observation was selected for practical reasons, and also we presumed that if an individual's blood pressure was elevated at the end of this time, it was elevated continually, for all practical purposes. No plan for elevating blood pressure has as yet been devised which meets with the approval of everybody. We realized that in the beginning. We thought the most important consideration was to adopt a standard method for obtaining blood pressure data and to employ it in every patient. This we have done. If we were to begin the study over again, I do not know of a better plan to adopt at this time. All the patients in this study had blood pressure readings in the resting horizontal position of 140/90 or more after forty-eight hours of hospitalization. The readings in the horizontal portion of the postural and cold blood pressure test, which are always the lowest in any portion of the test, have been regarded as the basal level. Other readings are taken for future comparison as well, such as when standing, and when stimulated by ice water both lying and standing (Fig. 1). Admission blood pressure levels taken by a physician as well as scattered levels taken mostly by nurses are also available during the entire hospital stay. In the early years, the postural and cold test was performed as described previously. In the latter half of the study it has been performed also almost immediately upon admission to the hospital. Follow-up studies have for the most part been carried out upon an ambulatory basis. Consequently, the percentage of patients having lowered blood pressure one or more years after operation is probably greater than we have judged it to be. We have recognized three degrees of lowering of blood pressure—first, in those patients whose diastolic levels in the horizontal position are below 90 mm. and 20 mm. or more lower on an ambulatory basis than they were preoperatively on a resting basis. The second degree of lowering is the same, 20 mm. or more but below 110 mm. and more than 90 mm. The third degree is 10 to 19 mm. lower and below 110 mm., provided the systolic pressure is lowered at least twice as much as the diastolic. These are very critical criteria, and upon this basis slightly less than one-half the patients have lowered blood pressure. We know that this is an understatement of the facts. On many occasions we have hospitalized patients for checkup studies or for operations of one sort or another following splanchnicectomy. When the postoperative studies are carried out on a comparable basis, almost invariably, significant changes in blood pressure are noted.

The other studies which were carried out in each case have to do with a careful evaluation of the cerebral, retinal, cardiac, and renal areas. All patients were studied by an opthalmologist and a cardiologist. Neurologists and urologists saw every patient when indicated, and additional studies were carried out if necessary. Routine studies included a careful history and physical examination, evaluation of the eyegrounds, electrocardiogram and seven-foot heart plate, intravenous pyelogram, urinalysis, urine concentration test, intravenous phenolsulfonphthalein test, and a sedative test. From time to time very detailed studies of small groups of cases were carried out to clarify problems related to the motor outflow of the sympathetic nervous system and the course of afferent pathways, utilizing skin temperature, skin resistance and plethysmographic

studies, balloon studies of the gastrointestinal tract, gastric secretory studies, studies of the motor and sensory innervation of the heart and of the biliary and renal tracts, and quantitative renal blood flow studies. In addition, detailed studies of the cardiovascular system by means of intra-arterial techniques for recording blood pressure levels and responses have been carried out by Wilkins and his associates.[18] We have also collaborated with other investigators studying various basic aspects of the physiology of the hypertensive patient with reference to renal pressor mechanisms and adrenal physiology.

TABLE II. NUMERICAL VALUE OF VARIOUS FACTORS WHICH INFLUENCE PROGNOSIS

	NUMERICAL VALUE OF EACH FACTOR
Cerebrovascular accident without or with minor residual Abnormal electrocardiogram Enlarged heart Impending congestive failure P.S.P.* less than 25% in 15 min., or less than 60% in 2 hr. Age 50 or over Mild angina	1
Cerebrovascular accident, with residual† Frank congestive failure, moderate angina P.S.P.* less than 20% in 15 min. Unsatisfactory response to sedation	2
P.S.P.* less than 15% in 15 min.	3
Nitrogen retention	4

Example 1	
Abnormal electrocardiogram	1
Cerebrovascular accident without residual	1
P.S.P.* 20% in 15 min.	1
Total	3 = Numerical grade
Example 2	
Abnormal electrocardiogram	1
Enlarged heart	1
P.S.P.* 10% in 15 min.	3
Total	5 = Numerical grade

*Phenolsulfonphthalein.
†Cerebral deterioration or persistent paralysis of arm and/or leg.

Having what we regard as adequate information upon each case, we have studied some 4,000 patients since 1938 and divided them into four groups, according to the amount of cardiovascular disease detected when first studied. A numerical value is assigned to various factors having a bearing on prognosis. These are summarized in Table II. The numerical values for each factor present are totaled, and this gives the numerical grade for the patient. Two examples of how to determine the numerical grade are given at the bottom of Table II.

If the numerical grade is less than 4 the patient will be in Group 1 or 2. If the numerical grade is 4 or more the patient will be in Group 3 or 4. The additional factors that determine the exact group of the patient are given in Table III. Thus the patients in Group 1 have persistently elevated blood pressure, with minimal or no eyeground changes and no abnormalities in the cerebral, cardiac, or renal areas. Those in the other groups have increasing amounts of cardiovascular disease. A sedative test is carried out on all patients. Three grains (180 mg.) of amobarbital (Amytal) sodium are given by mouth at 7:00, 8:00, and again at 9:00 P.M. Readings of blood pressure are taken every hour from 7:00 P.M. to 7:00 A.M. The lowest reading of diastolic pressure during the sedative test is taken to be the response to sedation. To be regarded as satisfactory, the diastolic level during the sedative test should fall to 90 mm. Hg or less in patients with resting levels between 100 and 119 mm. Hg. For patients with resting levels between 120 and 139 mm. Hg the response to sedation should be a fall to 100 mm. Hg or less. For those with resting levels of 140 mm. Hg or more, the diastolic level should fall to 110 mm. Hg or less. Otherwise, the response to sedation is regarded as unsatisfactory. Patients in both categories, surgical and medical, have been studied and classified in exactly the same fashion and can therefore be compared with respect to survival rates and mortality within the four groups.

VOL 1 195

TABLE III. CLASSIFICATION OF HYPERTENSIVE PATIENTS: CRITERIA FOR GROUPING

GROUP	NUMERICAL GRADE	OTHER FACTORS
1	Less than 4	Eyegrounds Grade 0 or 1 No changes in cerebral, cardiac, or renal areas
2	Less than 4	Eyegrounds Grade 0 or 1 with changes in cerebral, cardiac, and/or renal areas; eyegrounds Grade 2, 3, or 4 with or without changes in cerebral, cardiac, or renal areas
3	4 or more	Resting diastolic level below 140 mm.; changes are present in cerebral, cardiac, and/or renal areas but they do not include the following: (a) Cerebrovascular accident with marked residual (b) Frank congestive failure (c) P.S.P. below 15% in 15 min. associated with a poor response to sedation
4	4 or more	Resting diastolic blood pressure below 140 mm. combined with one or more of the following: (a) Cerebrovascular accident with marked residual (b) Frank congestive failure (c) P.S.P. below 15% in 15 min. combined with a poor response to sedation. Patients with a resting diastolic level of 140 mm. or more.

There are so many variable factors in this disorder that it is most important to try to take as many as possible into consideration when attempting to evaluate a therapeutic measure. The general status of the cardiovascular system is a most important matter. This was first emphasized by Keith, Wagener, and

Barker,[19] who divided their patients into four groups according to the eyeground changes. Our method for dividing patients into four groups takes the entire cardiovascular system into consideration as well as blood pressure levels. It is more comparable to the methods of classification used by Hammarström and Bechgaard[20] and by Palmer, Loofbourow, and Doering.[21] Any of these methods for dividing patients into more comparable groups is adequate to show very clearly that the prognosis for patients is dependent primarily upon the status of the cardiovascular system. Another very important factor is the sex of the patient. Everything else being as comparable as possible, it is obvious that the prognosis for male patients is far less favorable than for females. Any estimation of the effect of therapy should take this factor into consideration. In the following discussion of the effect of splanchnicectomy upon the course of hypertensive disease, the data for the four groups will first be presented by means of mortality rates and survival curves with a statistical analysis of the results. The same data will then be presented for males and females separately. All the patients in Groups 2, 3, and 4 can be regarded as being in the complicated phase of hypertensive vascular disease, as defined by Dr. Perera, with those in Group 1 verging upon the complicated phase. From Groups 2, 3, and 4, 151 patients, who qualify as being in the accelerated phase on the basis of the eyeground changes, have been selected to illustrate the effect of splanchnicectomy upon this manifestation of the disorder.

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955

RESULTS: MORTALITY RATES AND SURVIVAL CURVES FOR NONSURGICALLY AND SURGICALLY TREATED PATIENTS

As has already been stated, the surgical maneuver which has been employed most commonly in the treatment of essential or malignant hypertension is lumbodorsal (thoracolumbar) splanchnicectomy. This operation has been used in 93 per cent of our surgically treated patients. Since this operation was first performed in 1938, a continuous follow-up program has been in operation. At this time it is possible to present statistics upon 2,070 hypertensive patients who were first seen five years or more ago and evaluated as just described. The longest period of follow-up of any patient in this group is sixteen years. That patient was the first to be operated upon by this technique and was in an accelerated phase of the disease, as evidenced by four diopters of papilledema. She has just had her sixteenth annual checkup and her cardiovascular system is essentially normal in every respect. She has never required supplementary medical treatment in the form of diets or drug therapy. All of these 2,070 patients were referred to me or my associates by their physicians for evaluation and advice regarding treatment by splanchnicectomy. Their general condition was found to be such that they were believed to be suitable risks for an operation of this sort. Operation was offered to these patients with varying degrees of enthusiasm according to their general cardiovascular status as a procedure which might favorably influence the course of their disease and increase their life expectancy. Of the total number of patients, 1,506 elected to undergo splanchnicectomy and 564 decided to follow a medical regime. This latter

group has been followed carefully and represents 87 per cent of all patients in this category brought under observation in the period 1938-1948. The 1,506 surgically treated patients have likewise been followed with equal interest and represent 95 per cent of all patients subjected to this operation during this time interval. We have lost track of the remaining patients. During this time other

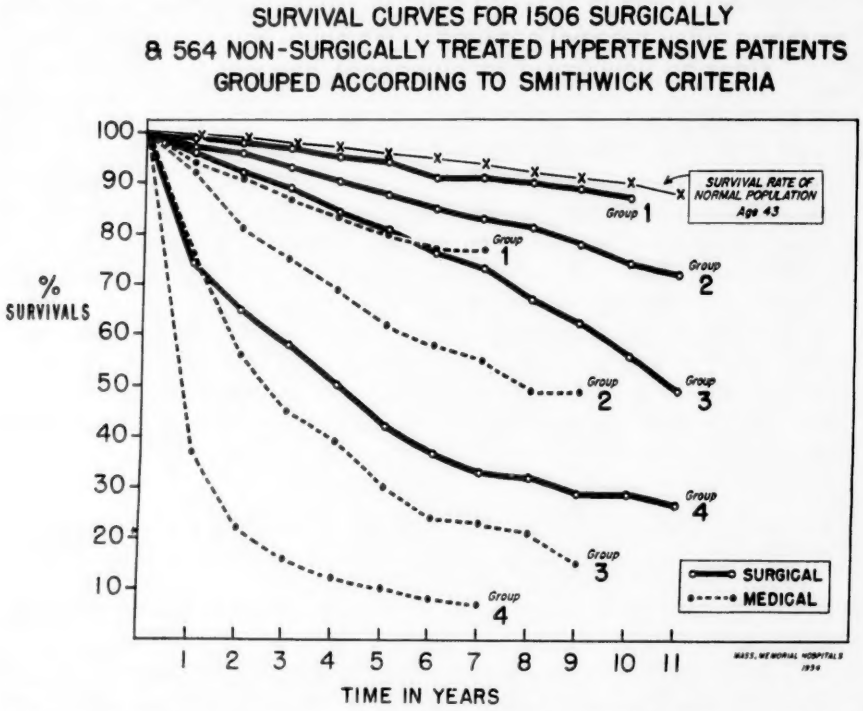

Fig. 2.—Survival curves for patients grouped according to Smithwick criteria. These curves have been constructed using the actuarial method. They serve to emphasize the marked differences between the surgical and the nonsurgical groups. Although some of the patients have been followed for as long as fifteen years, the curves have not been carried beyond the eleven-year mark in any case, because either the number of cases is too small to be significant or no further deaths occurred. A survival curve of the normal population is included for comparison.

patients who were too advanced for surgical treatment were seen. Operation was not recommended for these patients. This discussion therefore deals with approximately 90 per cent of all patients studied during a ten-year period who were in good enough shape to justify surgical treatment. Those who for one reason or another decided against operation serve as a control series* for the operated patients.

*All the patients in both the medical and the surgical series were first seen at least five years ago and at most sixteen years ago, so that for the vast majority of the follow-up period none of the patients could have received the more recently developed hypotensive drugs. Of the nonsurgically treated patients who have been followed by us, which represents about 10 per cent of the total number, the great majority have been treated by the more recently developed drugs during the past two or three years. I can only presume that the patients who are being treated by their own doctors in various parts of the world are likewise receiving newer drugs as they appear on the market. In so far as the surgical series is concerned, about one-half the patients have had some sort of a supplementary regimen, usually consisting of a moderate restriction in the intake of salt and fat and the use of one of the less oxic drugs, such as one of the Rauwolfia preparations.

The mortality rates for the two series have been calculated at the end of five years of follow-up since that is the shortest period of observation for any patient. These are presented in Table IV for each of the four groups. These data are also summarized in the form of survival curves in Fig. 2. These curves have been carried out for periods of observation of up to ten years when the numbers of cases permit or to the point of the last known death in any group. The average age of the surgical patients was 42 years, of the medical cases 46 years, and of the group as a whole 43 years. Seventy per cent of the patients were 40 years of age or older and 25 per cent were over the age of 50. We have tended to be more conservative in offering surgery to patients over the age of 50, but in recent years have been operating upon more elderly patients than in the early years of this study. Patients over 50 and in a rare case over 60 who are not doing well on a medical regimen may still be satisfactory surgical risks and may benefit greatly by surgical treatment. There were 1,034 males and 1,036 females. A survival curve for the population as a whole at the age 43 of a comparable sex distribution is included in Fig. 2 for comparison with the curves of the patients with the varying degrees of cardiovascular disease in the two series of cases. The mortality rates and the survival curves together with the analysis of their statistical significance have been calculated and prepared under the supervision of Mr. John Alman, Director of Statistical and Research Services at Boston University. The tremendous statistical significance of the difference in outlook for the patients in the various groups in the two series, in favor of the surgically treated cases especially in Groups 2 and 3, is clearly apparent. It indicates to us that splanchnicectomy has been very well worth while, and in recent years we have urged patients in Groups 2 and 3 to undergo surgical treatment, believing that we had a sound basis for recommending splanchnicectomy rather than offering it as a therapeutic measure which might possibly be helpful. Conclusions similar to these, based upon a study of a smaller series of cases, were published in 1953.[22]

RESULTS: MORTALITY RATES AND SURVIVAL CURVES FOR NONSURGICALLY AND SURGICALLY TREATED PATIENTS ACCORDING TO SEX

The foregoing discussion indicates very clearly that vascular disease, as judged by the changes in the cerebral, retinal, cardiac, and renal areas, is a crucial factor in influencing the prognosis of hypertensive patients. Another factor of importance is sex. This has been apparent ever since physicians began to study the influence of hypertension upon life expectancy. The fact that males do not tolerate hypertension as well as females was brought out very clearly by Janeway,[23] in what may be regarded as the first important clinical evaluation of the prognosis for patients with hypertensive vascular disease to be undertaken after the introduction of the sphygmomanometer. In our follow-up study we have been aware of this factor for many years but have not been in a position to discuss it from a statistical viewpoint until the number of patients became large enough to take both vascular disease and sex into consideration. It now appears valid to evaluate the prognosis and the influence of treatment upon the course of hypertensive vascular disease for males and females considered separately.

To do this, the cases considered in the preceding portion of this discussion have been divided into two groups, according to sex. There were 1,034 males and 1,036 females. Each group has been subdivided into four on the basis of the status of the cardiovascular system, as already described. The mortality rates for the male patients in both the medical and the surgical series are contained in Table V. The same information for female patients is presented in Table VI. A study of these statistics indicates that regardless of the form of treatment, the prognosis for females is better than for males. For male patients,

TABLE IV. FIVE-YEAR MORTALITY RATES FOR 1,506 SURGICALLY AND 564 NONSURGICALLY TREATED HYPERTENSIVE PATIENTS

GROUP	MEDICAL SERIES		SURGICAL SERIES		STATISTICAL ANALYSIS		
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)	CHI^2	p	SIGNIFICANCE
1	70	20	179	6	9.22	<0.005	Highly significant
2	243	38	896	12	86.4	<0.001	Highly significant
3	135	70	294	19	100.1	<0.001	Highly significant
4	116	90	137	58	29.4	<0.001	Highly significant

there is a very marked difference in prognosis according to the treatment employed. In all four groups the mortality rates for patients who were operated upon are significantly lower than are those for the patients in the medical series. This is especially true for patients in Groups 2 and 3. The mortality rates for female patients treated surgically are likewise lower in all four groups, but the differences observed are not as great as for male patients and are highly significant from a statistical viewpoint in Groups 2 and 3 only. This confirms our impression to date that splanchnicectomy has exerted its greatest effect on prognosis when operation is performed soon after important changes in the vascular system begin to make their appearance (Group 2) and even when the abnormalities are quite advanced and widespread (Group 3). It also is apparent that it is a mistake to withhold surgical treatment until patients progress to Group 4 since, regardless of what is done, the mortality rates are very high. In most Group 4 patients the damage to the vascular system is too severe, and no form of treatment currently available or which may become available in the future can be expected to overcome this handicap. I believe that the ideal time to utilize surgery is when patients are found to be in Groups 2 and 3.

The medical armamentarium now available for the treatment of patients with hypertensive vascular disease is certainly greater than it was twenty-five years ago, or even five years ago. There is a growing impression that it is more effective. It will take many years to prove that this is the case. Even if it proves to be more effective, it certainly has become much more drastic. Treatment by rigid diets and the use of multiple drugs is difficult for the physician to control and hard for patients to follow for long periods of time. There are also

VOL. 1 1955

an increasing morbidity and mortality associated with medical treatment, especially in patients having important changes in the vascular system. This will have to be taken into consideration. I seriously doubt that even if medical treatment should prove to be much more effective than it has in the past, it will be as satisfactory a method for the long-range management of patients with the more severe forms of hypertensive vascular disease, as is splanchnicectomy alone or, when necessary, combined with far less drastic dietary and drug therapy.

TABLE V. FIVE-YEAR MORTALITY RATES FOR 1,034 MALES

GROUP	MEDICAL SERIES		SURGICAL SERIES		STATISTICAL ANALYSIS		
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)	CHI^2	p	SIGNIFICANCE
1	36	28	77	8	6.50	<0.01	Significant
2	131	49	387	18	46.7	<0.001	Highly significant
3	91	77	150	22	67.6	<0.001	Highly significant
4	79	96	83	60	28.2	<0.001	Highly significant

TABLE VI. FIVE-YEAR MORTALITY RATES FOR 1,036 FEMALE PATIENTS

GROUP	MEDICAL SERIES		SURGICAL SERIES		STATISTICAL ANALYSIS		
	NO. CASES	MORTALITY (%)	NO. CASES	MORTALITY (%)	CHI^2	p	SIGNIFICANCE
1	34	12	102	4	1.59	<0.2	Not significant
2	112	26	509	8	28.4	<0.001	Highly significant
3	44	55	144	17	23.5	<0.001	Highly significant
4	37	76	54	56	3.02	<0.08	Not significant

Having followed a very large number of patients for up to sixteen years and many patients for ten to fifteen years after operation, we have found splanchnicectomy alone or combined with a reasonable medical regimen a very satisfactory way to control hypertensive vascular disease, from the viewpoint of both the patients and the physicians. Splanchnicectomy protects the patient against lapses of medical therapy. Checkup examinations are needed much less frequently. Patients are able to lead a more normal existence since reasonable precautions regarding salt and fat intake and the use of one of the less toxic drugs, when drugs are necessary, are all that are needed in the great majority of cases when splanchnicectomy alone is not sufficient. Splanchnicectomy renders patients with the more severe forms of hypertensive vascular disease more susceptible to dietary and drug therapy, as well as to rest. It commonly renders patients less tense and makes it easier for them to adopt a better philosophy toward their disorder and toward life in general. So many hypertensive patients are dynamic individuals, often extremely meticulous and conscientious,

who find it difficult to relax. They often have too many irons in the fire, feel that they are the only ones who can do things properly, and are unable to delegate authority to others. They feel either that they are the only ones who can perform a particular job adequately or else that nobody can do it as well. Consequently, they have to do it themselves. To correct this general pattern of thinking of the hypertensive patients is an important part of any long-range therapeutic effort.

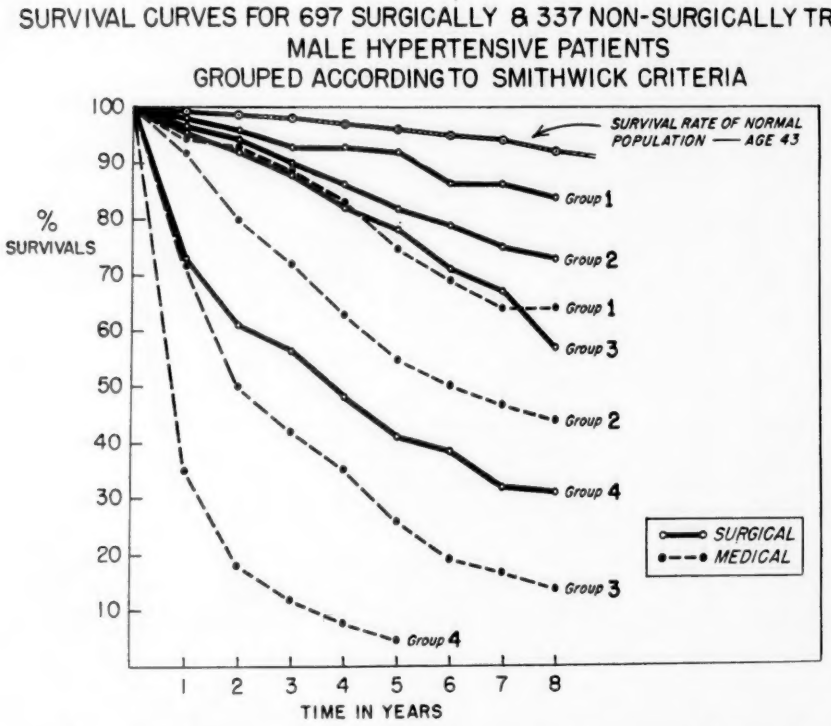

Fig. 3.—Survival curves for 1,034 male patients. These can be compared with those for male and female cases combined (Fig. 2) and with those for female patients only (Fig. 4). See Tables IV, V, and VI for mortality rates corresponding to Figs. 2, 3, and 4.

The striking differences in the mortality rates for male and female patients treated surgically when compared with those treated medically are further emphasized by the survival curves contained in Figs. 3 and 4. Fig. 3 deals with male and Fig. 4 with female patients. Included in each is a survival curve for the normal population of the same sex and age. These data indicate clearly how unfavorably the vascular changes in each of the four groups affect life expectancy. It also shows the importance of instituting therapy early in the disease if anything approaching a normal life expectancy is to be achieved for these patients.

The Accelerated Phase.—As Dr. Perera[1] has indicated, vascular changes progress very rapidly in certain hypertensive patients and, unless something is

done to arrest them, death may ensue in weeks, months, or one or two years from the time the patient is first seen. One of the most ominous indications of rapid progression is papilledema. Of patients having this sign, Keith, Wagener, and Barker[19] found that about 80 per cent were dead in one year, 90 per cent in two years, and almost 100 per cent by the end of five years. Of the 2,070 patients who form the basis for this report, all those having papilledema were analyzed separately. There were 151 cases, or 7 per cent of the total number. In Table VII these patients are arranged according to whether they were in the medical or the surgical series and according to renal function as well. The mortality rates are calculated for each of the five years of follow-up. Of the

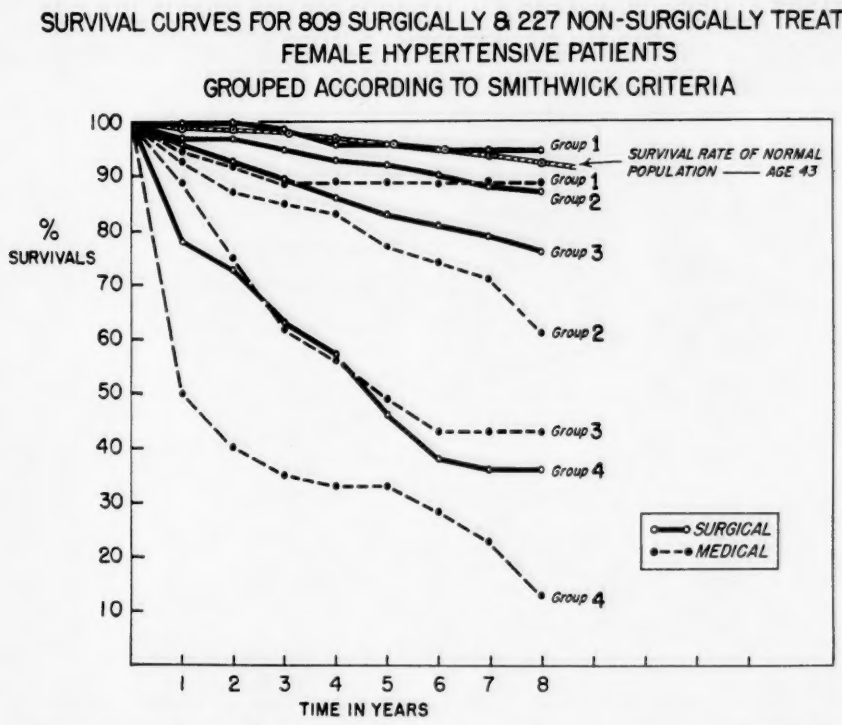

Fig. 4.—Survival curves for 1,036 female patients. These can be compared with those for male and female cases combined (Fig. 2) and with those for male patients only (Fig. 3). See Tables IV, V, and VI for mortality rates corresponding to Figs. 2, 3, and 4.

thirty-seven patients in the medical series, thirty-six or 98 per cent were dead at the end of five years. Of the 114 patients in the surgical series, fifty-five or 48 per cent were dead at the end of five years. The status of the renal function did not seem to make much difference in the medical series, whereas in the surgical series, the prognosis appeared to be very definitely related to renal function in the sense that if the latter was normal or only slightly decreased at the time of operation, the outlook was much better than when kidney function was moderately or markedly reduced. Although the number of cases in the medical series is small, the implication is that the treatment employed had little effect upon

the mortality rate. Splanchnicectomy definitely appeared to slow the progress of the disease and to prolong life. Because of the small number of patients in the medical series, those having normal or slightly reduced renal function have been grouped (I) together, while those having moderate to marked reduction have been arranged similarly (II). Survival curves have been drawn upon this basis. These are shown in Fig. 5 together with comparable data for the surgical cases. In constructing these curves, the mortality rates were calculated at the end of each year. The more complicated actuarial method, which was used to construct the survival curves presented earlier in this report (Figs. 2, 3, and 4), was not employed. Fig. 5 brings out the fact that the prognosis for patients having papilledema and a comparable renal function status was much better if they were treated surgically. If operation was performed when kidney function was normal or only slightly reduced, the prognosis was very much better than in patients having moderate or marked impairment of renal function.

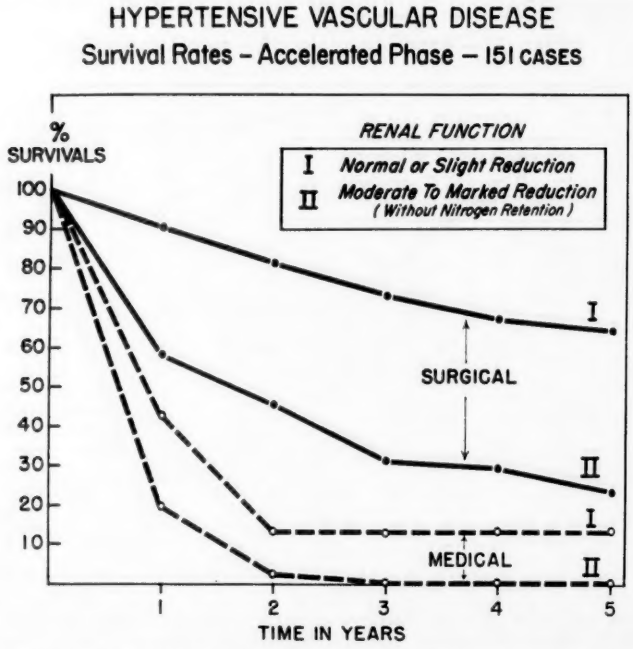

Fig. 5.—Cases having normal or slightly reduced renal function are grouped together, and the survival curves for these patients are labeled *I*. The mortality rates for the surgical cases for each of the five years were 9 per cent, 18 per cent, 26 per cent, 32 per cent, and 35 per cent. The corresponding figures for the medical series were 57 per cent, 86 per cent, 86 per cent, 86 per cent, and 86 per cent. Patients having moderately or markedly reduced kidney function form Group *II*. The mortality rates at yearly intervals were 41 per cent, 54 per cent, 68 per cent, 70 per cent, and 76 per cent for the surgical cases and 80 per cent, 97 per cent, 100 per cent, 100 per cent, and 100 per cent for the medical patients. See Table VII for the yearly mortality rates for each of the four categories of renal function.

SUMMARY: "WHAT DO YOU DO FOR HYPERTENSION?"

In the foregoing discussion, an attempt has been made to summarize the experience my associates and I have had with the management of hypertensive

vascular disease during the past twenty years. The surgical approach to the problem has been the basis for this extensive clinical investigation of splanchnicectomy as a therapeutic measure. Approximately 4,000 patients have been studied carefully. Those who were first seen five years or more ago form the basis for this report. In addition to the evaluation of surgery, many patients have been treated medically and followed for long periods of time. We have also observed many patients in whom both medical and surgical measures were employed. In other cases, no treatment was instituted. This has been an unusual experience for all of us, for the physicians concerned as well as the surgeons.

TABLE VII. HYPERTENSIVE CARDIOVASCULAR DISEASE: MORTALITY RATES IN ACCELERATED PHASE

TIME (YEARS)	RENAL FUNCTION*	MEDICAL SERIES			SURGICAL SERIES		
		NO. CASES	DEAD	MORTALITY (%)	NO. CASES	DEAD	MORTALITY (%)
1	Normal	4	3	75	49	3	6
2			4	100		7	14
3			4	100		10	20
4			4	100		13	27
5			4	100		15	31
1	Slight reduction	3	1	33	28	4	14
2			2	67		7	25
3			2	67		10	39
4			2	67		12	43
5			2	67		12	43
1	Moderate reduction	6	5	83	12	2	17
2			6	100		5	42
3			6	100		8	67
4			6	100		8	67
5			6	100		8	67
1	Marked reduction	24	19	79	25	13	52
2	without nitrogen		23	96		15	60
3	retention		24	100		17	68
4			24	100		18	72
5			24	100		20	80
	Total	37	36	97	114	55	48

*Renal function was judged by the output of phenolsulfonphthalein in fifteen minutes after intravenous injection of 1 c.c. of the dye. Normal, 25 per cent or more; slight reduction, 20 to 24 per cent; moderate reduction, 15 to 19 per cent; marked reduction, less than 15 per cent without nitrogen retention.

Our basic objective was to determine whether splanchnicectomy was of value in the management of hypertensive vascular disease. We have convinced ourselves that this is the case, and have indicated the circumstances under which it has been most helpful. At the same time we have also found that medical measures, especially diets low in sodium content and drugs which have a sedative or hypotensive effect, are of real value in the management of this disorder. We believe that the best interests of patients with severe forms of hypertensive

vascular disease are served by taking advantage of what both medicine and surgery have to offer, fully realizing that at this time no form of therapy can be regarded as specific for the great majority of patients. What we *do* for hypertension is briefly summarized in the following paragraphs.

1. If one is dealing with patients in an early stage of the disorder, careful observation with a yearly checkup of the cardiovascular system is indicated. This statement refers to patients having intermittent hypertension or, in other words, to those having elevated blood pressure when ambulatory which falls within the normal range after short periods of rest. The great majority of these patients have no evidence of cardiovascular disease. There are occasional exceptions (Fig. 1). When this is found to be the case, treatment should be instituted, since our objective is to prevent the complications of cardiovascular disease, to prolong life, and to relieve symptoms. If cardiovascular changes are detected, we hope to be able to cause them to regress to normal if possible. For most patients in the stage of intermittent hypertension, the problem is to prevent the development of vascular disease or to detect its presence promptly. If a satisfactory form of prophylactic treatment were available, this would be the ideal time to use it. When active treatment is indicated, we usually employ medical measures first but resort to splanchnicectomy when necessary or when it is considered to be more appropriate (Fig. 1).

2. For patients in the later stages of the disorder, namely, those having continually elevated blood pressures after short periods of bed rest, the treatment employed depends first of all upon the amount of disease detected in the vascular system and, in the second place, upon the sex of the individual. Thus Group 1 females are placed upon a medical regimen, and surgery is employed only if this proves unsatisfactory or impracticable or in young females desiring children in whom pregnancy would otherwise appear to be hazardous.

Group 1 males are informed of the fact that our experiences to date indicate that surgical treatment is preferable. The evidence upon which this statement is based is carefully explained to them. They are also told that medical measures are available today which appear to be more effective than they were five or more years ago and that they may elect this form of treatment providing they realize that it means complete cooperation on their part as to the following of diets and the taking of drugs. It also requires the close cooperation of physicians involved and the necessity of frequent checkup examinations. We also indicate that we are dubious as to whether medical management will prove to be the best in the long run, especially in male patients having high resting diastolic levels. For those who elect a medical regimen, surgery is held in abeyance to be employed if the program proves to be ineffective or impracticable.

3. Surgery is recommended as the treatment of first choice for both male and female patients falling into our Groups 2 and 3. The statistical evidence upon which this advice is based is explained carefully to the patients and the doctors concerned. These are patients who are, in most instances, rapidly approaching the stage of the disease where all therapeutic measures of both a medical and surgical nature are relatively ineffective (Group 4). We feel that

VOL
1
195

it is important to do all we can to prevent cases in Groups 2 and 3 from progressing to Group 4. In spite of the fact that present-day medical measures may prove to be more effective than they have in the past, we have no evidence as yet that this will be the most satisfactory method to handle patients of this sort for long periods of time. The advanced cardiovascular changes which are present in many of these patients, especially those in Group 3, make them undesirable candidates for intensive treatment by the more potent and potentially toxic drugs. Consequently, we recommend surgery, to be supplemented by a less drastic medical regimen when necessary, as the best form of treatment for these patients at the present time. For those who do not elect to be operated upon, an appropriate medical regimen for the individual patient is instituted. As a matter of fact, the vast majority of patients in this stage of the disorder referred to us for consideration of surgery have already had an adequate trial of medical management.

4. The long-range management of both male and female patients in Group 4 has been very discouraging. In spite of the fact that splanchnicectomy has favorably affected the survival rates of patients of both sexes, especially of males, the late results are very discouraging. All these patients require the intelligent utilization of every therapeutic measure we have at our disposal. Many are found to be poor risks and unsuited for splanchnicectomy. When the operative risk is not deemed prohibitive and when the changes in the cardiovascular system, especially those in the renal area, do not indicate an absolutely hopeless prognosis, splanchnicectomy is recommended to the patient as offering some chance for improvement. Our experience with the management of the late stage of hypertensive vascular disease has convinced us that splanchnicectomy should not be regarded as a measure to be employed as a last resort.

5. In the management of patients in an accelerated phase of hypertensive vascular disease, splanchnicectomy has been of distinct value, especially in patients who still have normal or only slightly reduced kidney function as judged by phenolsulfonphthalein excretion. Under these circumstances, we believe it to be the treatment of first choice. The prognosis for patients having moderately or markedly reduced renal function is grave, regardless of the therapy employed.

REFERENCES

1. Perera, G. A.: Hypertensive Vascular Disease: Therapeutic Principles and Objectives, J. CHRON. DIS. **1**:472, 1955.
2. Peet, M. M.: Splanchnic Section for Hypertension: A Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1**:17, 1935.
3. Bright, R.: Reports of Medical Cases Selected With a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy, London, 1827, Longman, Rees, Orne, Brown, and Green.
4. Bright, R.: Cases and Observations Illustrative of Renal Disease Accompanied With the Secretion of Albuminous Urine, Guy's Hosp. Rep. **1**:338, 1836.
5. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease With Contracted Kidney "Arterio-capillary Fibrosis," Med.-Chir. Trans. **55**:273, 1872.
6. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Nonhypertensive Individuals, Am. J. Path. **13**:679, 1937.
7. Goldblatt, H.: Studies on Experimental Hypertension. XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, Am. J. Clin. Path. **10**:40, 1940.

8. Page, I. H.: Production of Persistent Arterial Hypertension by Cellophane Perinephritis, J.A.M.A. **113**:2046, 1939.
9. Smith, H. W.: Studies in the Physiology of the Kidney, Porters lectures, series 9, Lawrence, Kansas, 1939, University of Kansas, University Extension Division, pp. 106.
10. Talbot, J. H., Castleman, B., Smithwick, R. H., Melville, R. S., and Pecora, L. J.: Renal Biopsy Studies Correlated With Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, J. Clin. Invest. **22**:387, 1943.
11. Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to the Hypertensive State, J.A.M.A. **121**:1256, 1943.
12. Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to the Hypertensive State. II. The Adequacy of the Renal Biopsy as Determined From a Study of 500 Patients, New England J. Med. **241**:729, 1948.
13. Smithwick, R. H., and Castleman, B.: Some Observations on Renal Vascular Disease in Hypertensive Patients Based on Biopsy Material Obtained at Operation. Hypertension. A Symposium, Minneapolis, 1951, University of Minnesota Press, pp. 199.
14. Castleman, B.: Causes of Essential Hypertension in Man as Elucidated by Anatomicopathological Investigation in Humans. A Symposium on Essential Hypertension, The Commonwealth of Massachusetts, 1951, pp. 102.
15. White, J. C., Smithwick, R. H., and Simeone, F. A.: The Autonomic Nervous System, ed. 3, New York, 1952, The Macmillan Company, pp. 569.
16. Smithwick, R. H., Chapman, E. M., Kinsey, D., and Whitelaw, G. P.: The Human Heart Rate: Some Observations and Deductions Based Upon the Effect of Removing Portions of the Sympathetic Nervous System in Men, Surgery **26**:727, 1949.
17. Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension, Surgery **7**:1, 1940.
18. Wilkins, R. W., Culbertson, J. W., and Smithwick, R. H.: The Effects of Various Types of Sympathectomy Upon Vasopressor Responses in Hypertensive Patients, Surg., Gynec. & Obst. **87**:661, 1948.
19. Keith, N. M., Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension; Their Course and Prognosis, Am. J. M. Sc. **197**:332, 1939.
20. Hammarström, S., and Bechgaard, P.: Progress in Arterial Hypertension. Comparison Between 251 Patients After Sympathectomy and a Selected Series of 435 Non-operated Patients, Am. J. Med. **8**:53, 1950.
21. Palmer, R. S., Loofbourow, D., and Doering, C. R.: Prognosis in Essential Hypertension. Eight Year Followup Study of 430 Patients on Conventional Medical Treatment, New England J. Med. **239**:990, 1948.
22. Smithwick, R. H., and Thompson, J. E.: Splanchnicectomy for Essential Hypertension. Results in 1,266 Cases, J.A.M.A. **152**:1501 (Aug. 15) 1953.
23. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**:755, 1913.

VOL. 1 1955

HYPERTENSIVE VASCULAR DISEASE: THERAPY WITH MODERN DRUGS AND ITS LIMITS

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IN HIS leading article in this JOURNAL, Perera has posed the crucial questions facing the physician upon whom responsibility for treating a hypertensive patient rests: "What am I really doing? Is it safe? Is it worth the effort? What is the evidence? Why should I do it? How can I do it?" While these questions reflect a healthy skepticism on the subject, they also show an optimism hard to find a few years ago. We have come a long way in four years, for then the questions were: "What little can I do to treat this patient with hypertension other than by 'supportive' measures?" or, in reference to neurosurgery, "Should hypertension be treated and, if so, will it do any good?" The inability of physicians to bring down the blood pressure in every case by any procedure led to a dependence upon rest, sedation, freedom from worry, reassurance, relaxation, diets of all varieties, psychotherapy, and teaching a patient to live with his disease, none of which helped much in severe stages of the disorder and none of which was very specific. It also led to an attitude of mind which was a natural human rationalization of our therapeutic ineptitudes: hypertension, once established, perhaps was "essential" to blood flow through various organs, and dire ischemic consequences might attend its reversal. One is reminded of the old expression, "laudable pus."

The advent of the neurosurgical approach with its incontrovertible demonstration of reversal of the disease in *some* patients pointed toward disproof of this attitude, except in those with severe secondary complications or borderline renal function. The revival of dietary salt restriction after many years' lapse added another, often minimal, increment to therapeutic measures. Thus, before the advent of modern drugs, it became obvious that vigorous surgical and dietary treatment allowed *some* individuals in severe stages to live beyond their expected years with a lower or normal blood pressure without ischemic manifestations. If this were true for some, it could be true for almost all. The era of "pills, powders, and promises" was superseded by one in which measures, albeit vigorous ones, appeared to be a bit more specific. But controlled studies by placebos were the rule, and the degree of significance of diastolic depression, either 12, 15, or 20 mm. Hg, was argued back and forth.

When hydralazine was first used five years ago, the numbers of patients responding by sustained lower blood pressure increased markedly but not enough. While the effect was greater than could be achieved with former measures, one-third of the treated patients were resistant. We noticed, however, that those whose sympathectomies had failed, pressurewise, responded well. Shortly thereafter, prolonged chemical sympathectomy became possible, and the proportion responding by significantly lower blood pressures caused by both new agents (methonium salts and hydralazine) increased to about 100 per cent. Placebos were no longer needed and, in fact, became dangerous; the question of the significance of diastolic depression disappeared, for it was not uncommon to observe systolic pressures controlled at or below levels where diastolic pressures had been, without ischemic consequences. The natural result was a radically new attitude; since blood pressure can be kept low, is this going to change the disease? Will we make it worse, and if so, under what conditions? These questions can now be answered in the main.

VOL.
1
1955

Because our personal experience with other forms of therapy was disappointing in general in that the more severe forms of the disease failed to be influenced uniformly, the present discussion will be largely confined to the use of modern drugs. It is admittedly one-sided, but is based on data on 400 patients, most of them in complicated or accelerated phases of the disease. We must start with one fundamental point of reference. There are presently available enough potent antihypertensive agents to lower the blood pressure of any hypertensive patient to almost any desired level, if used properly. In this light we can then consider the questions.

What am I really doing? Arterial hypertension of all varieties not secondary to increased cardiac output, blood viscosity, and blood volume is the result of excessive generalized vasospasm with a heart able to pump the increased load. The relief of hypertension depends, therefore, on the prevention or reduction of excessive vasospasm. A lower level of blood pressure secondary to any disturbance not dependent upon the relief of generalized vasospasm is unphysiologic. A lower level of blood pressure achieved by any mechanism dependent upon the relief of generalized vasospasm is physiologically sound, although not necessarily sound biochemically. Blood pressure can be lowered to any desired level by hemorrhage, trauma, cardiac damage, anemia, but these methods are "unphysiologic" and "unbiochemical." On the other hand, the modern chemotherapeutic agents *appear*—and we must stress the word—to lower blood pressure "physiologically" by interfering with pathogenetic mechanisms, and some of them *appear* on the surface to interfere with basic biochemical mechanisms involved in the disturbance. Whether or not they restore altered biochemical reactions to normal or interfere with an abnormal reaction to produce further abnormality and an appearance of normality is not yet known. Neurosurgery can occasionally cause the appearance of normality.

To understand what we are really doing with modern antihypertensive drugs, we should examine the known and possible actions of the drugs themselves on which to evaluate the result in the patient. Only pure available com-

pounds will be discussed. If a physiologist were asked to list the various methods for producing generalized vasospasm in animals, he would group them under three headings: through nervous mechanisms, through humoral, possibly nephrogenic mechanisms, and through adrenocortical mechanisms. If a clinician were asked to list the various diseases and disorders associated with generalized vasospasm and hypertension in man, he would group them under the same three headings.

The actions of most of the following specific drugs, being partly known, will be discussed briefly.

Drugs Acting on Autonomic Nervous System.

(a) *On mid-brain:* Reserpine acts on the posterior hypothalamus or on some prehypothalamic pathways, causing inhibition of central sympathetic centers. The net result is slight parasympathetic overactivity. The drug in usual doses is a mild "sympatholytic" and a mild antihypertensive agent. It is cumulative and slowly excreted. As far as is known, when we give it we produce the effects of partial sympatholysis as well as a curious type of sedation and freedom from anxiety quite reminiscent of prefrontal lobotomy. Strangely enough, it apparently can also cause anxiety and rarely even psychosis.

In the hypertensive patient, the effects are variable. In general, patients in milder stages of the disease respond fairly well, in severe stages, poorly; but there are exceptional individuals in severe stages who respond well and many in milder stages who respond poorly. This agent should not be used in patients whose treatment is mandatory for life without close and careful supervision, for a false sense of security can be given the physician doing something, while the disease progresses rapidly toward its end stages. For this reason, it can be dangerous.

(b) *On hind-brain:* Protoveratrine, a mixture of A and B, acts on carotid sinus and body receptors apparently through a reflex arc via the glossopharyngeal nerve to the vasomotor centers in the medulla. The net peripheral effect is parasympathetic stimulation, with slow pulse, vasodilatation, fall in blood pressure, nausea, and vomiting. When we give it, we apparently stimulate the pressor receptors to greater activity. Unfortunately the hypotensive dose and that which will cause vomiting are close, the two effects cannot be separated by chemical purification of the two agents, and tolerance appears within several hours, requiring omission of the drug for several more.

In the hypertensive patient, the effects are variable. Some respond by intermittent normotension, others with little change until vomiting prevents further increase in dosage. It is our clinical impression, based on no experimental evidence, that this drug acts less "physiologically" on one portion of the hypertensive process than do others—although none is truly "physiologic."

(c) *Ganglionic-blocking agents:* These drugs block nerve transmission across autonomic ganglia, probably by competitive inhibition with acetyl choline or analogous substances. All are quaternary ammonium compounds, containing tetracovalent nitrogen, a configuration which influences nerve transmission. They differ one from another only in their durations of action and possibly in

their affinities for different ganglia. When we give them to a patient, we cause sympatholysis at the price of parasympatholysis. They are excreted fairly rapidly, requiring repeated doses.

In the hypertensive patient, we are *partially* blocking that portion of the vasospasm caused by neurogenic (sympathetic) impulses. Therefore, the proportionate influence of neurogenic vasoconstriction contributing to the total picture (which may vary from 15 to 85 per cent) is partially opposed by the drug. The effects on hypertension are thus as variable as are those following other forms of sympathectomy, chemical or surgical. Some patients respond well with intermittent vasodilatation, others apparently not at all. In general, the more severe the disease the less is the response.

The type of blocking agent used is a matter of individual preference, both for patient and physician. All of them produce parasympatholysis to greater or lesser extent; some act for slightly longer periods than others. Even the longest acting, a new unnamed drug (Su-3088), by itself will not, in our experience, control the more severe forms of hypertension. The addition of a drug acting on a mechanism other than the nervous is required.

(d) *Neurosurgery:* Surgical sympathectomy provides more definitive but more localized sympatholysis than do the blocking agents, without annoying parasympatholysis. In the hypertensive patient, we are removing neurogenic vasoconstrictor impulses from most of the lower half of the body. In so far as neurogenic influences contribute to the picture, reversal may be expected, plus an added unknown increment which varies from person to person.

Drugs Acting on Vascular Smooth Muscle.—The substituted hydrazines, hydralazine and its derivatives, act on *constricted* vascular smooth muscle. Because of their prolonged action they are unique agents. When we administer them in adequate doses, we are probably interfering with smooth muscular constriction at a very basic level. There is some confusion in the literature regarding their modes of action; therefore, it is pertinent to list known functions and to stress what they do not do (Table I).

In the hypertensive patient, we are opposing excessive vasospasm at the muscular level. We are probably not producing a significant degree of sympatholysis. The results are variable in proportion to the severity of the hypertension and to that component which is nonneurogenic and probably nonadrenocortical. By exclusion, the nephrogenic or humoral vasospastic factor is probably opposed.

Procedures Acting on Adrenocortical Influences.—Restriction of dietary sodium may affect the adrenal cortex (by depletion of lipid). On the other hand, the net effect appears to be a reduction in the reactivity of vascular smooth muscle to sympathetic stimulation and norepinephrine. It is possible, but still unproved, that unmyelinated nerve transmission is reduced. In the hypertensive patient, low-salt diets may occasionally reduce blood pressure by themselves, rarely to the degree attained by drugs, but marked potentiation of sympatholytic procedures (drugs, surgery) can occur. Adrenalectomy also depresses vascular reactivity.

VOL 1 195

TABLE I. SUMMARY OF PROPERTIES OF HYDRALAZINE OTHER THAN CARDIOVASCULAR

Basic Chemical Reactions in Vitro	
Metal binding	— complete for Fe^{3}, Cu^{2}, Sn^{2}, V^{5}
	— partial for Mn^{2}, Fe^{2}, V^{3}, Ni^{2}, Ag, Hg
	— none for Na, K, Be^{2}, Mg^{2}, Ca^{2}, Zn^{2}, Co^{2}, Cr^{2}, Cd^{2}, Al^{3}, As^{5}, Pb^{2}
Carbonyl reagent	— with pyruvate, acetaldehyde, acetate
	— not with glucose, lactic acid
Complex with SH	— with cysteine, glutathione, BAL, and other simple mercaptans
Protein binding	— with serum, arterial mash, egg albumin, polypeptides
	— not with casein, mixed amino acids
Antienzyme	— for histaminase(10^{-6}), stronger than guanidine, thiosemicarbazide; weaker than hydrazine, aminoguanidine; equal to semicarbazide
	— for DOPA decarboxylase, moderate (10^{-4})
	— for monamine oxidase, weak (10^{-3})
	— for succinic dehydrogenase, cholinesterase, polyphenol oxidase, none
Combination with	— no primary amines or simple amino acids
	— lyophilized angiotonin
Blocking Actions in Vivo	
Weak for epinephrine, norepinephrine, arterenone, tyramine, isoamylamine, angiotonin	
Strong for pherentasin, pervanadyl, cadmium, barium, pitressin	
Variable for serotonin according to species (weak in rat and dog, strong in cat)	
Blocking Actions on Rabbit's Arterial Strip	
Strong for pherentasin	
Weak for norepinephrine	
Vascular Reactions in Animals	
Dilates constricted vessels, renal, femoral, coronary; acts for many hours	
Does not dilate dilated vessels further (as in spinal animal)	
Abolishes constriction caused by Ba, pitressin, ephedrine, ergotamine, histamine, Privine	
Reactions in Man	
Lowering of plasma cholesterol	
No lowering of blood pyruvate or total carbonyl	
Apparent loss of Cr, Ti in urine	
Mild anemia	
? Histamine release	
Increases cardiac output, tachycardia	
Increases renal plasma flow	

When two drugs or procedures acting on two different mechanisms are used together, the vasospastic process is attacked at two levels. Clinically, two approaches have been found necessary in almost all severe cases, a tacit assumption that either the single basic pathogenetic influence is not being treated, or two influences combine to produce the disease. Apparently the neurogenic factor and vascular smooth muscle both must be affected for a favorable therapeutic response. The choices of the twin procedures are several: one of the neurogenically acting drugs and hydralazine, which we have found to be the most effective and least bothersome combination; neurogenically acting drugs and salt restriction; neurosurgery and hydralazine; neurosurgery and salt restriction; and in a few cases, all three types of measures. Adrenalectomy is hazardous and unnecessary, except where tumors exist.

Is it safe? The answer is "No!" if one assumes no toxicity, no care in administration, and no concern for the consequences of rapidly altering long-established hemodynamics. Any *potent* agent or procedure is unsafe in careless hands. On the other hand, control of vasospasm by drugs is reasonably safe when careful precautions are taken in the light of knowledge of their pharmacologies and of alterations associated with the hypertensive state. The theoretical hazards are threefold.

(1) Reactions and accidents resulting from lowering of the blood pressure are in the main probably secondary to organic vascular changes in vital areas, especially the coronary and cerebral arteries. Hypertension appears to promote accidents in these areas; a change in hypertension may likewise promote vascular occlusions. Fortunately, arterial thrombosis is rare; we have seen only three such accidents accompanying the use of these drugs. By slowly changing hemodynamics they may be largely avoided. The procedure is considerably safer than are the consequences of the disease. Thrombosis or ischemia in a vital area is therefore the result of *lack* of participation of the artery supplying that area in the general vascular dilatation. The cause of the failure to relax lies in the nature of the sclerotic process. It is possible that small areas of ischemia can thus temporarily appear which do not become apparent clinically and which regress with the opening of collaterals. We have seen Leriche's syndrome, however, improve symptomatically twice in the face of a markedly lowered blood pressure, an unexpected occurrence.

A further hazard is the induction of uremia in azotemic patients with severe organic renal vascular changes. A compromise level of blood pressure may be attained, sufficiently low to prevent heart failure, but high enough to allow adequate filtration through damaged kidneys. We have not seen uremia induced in the absence of azotemia, and only rarely is it caused by careful and partial lowering of blood pressure, unless, by chance, therapy produces an unexpected and rapid hypotension. Hemorrhage or hyponatremia, for example, may increase the sensitivity of the vascular bed to ganglionic blockade. As methonium compounds are excreted in the urine, excessive amounts may accumulate in azotemic states; should anuria supervene, none will be excreted.

(2) Fatalities due to the drugs themselves are rare. A condition which we may call "ganglionic-blockade disease," characterized by rapidly advancing pulmonary insufficiency with autopsy findings of acute interstitial fibrosis of the lungs, has caused four of our deaths. It has been reported in the British literature following the use of parenteral hexamethonium chloride; in our cases poor control of malignant hypertension was the rule. The condition may be mechanical (repetitive bouts of asymptomatic localized pulmonary congestion or edema) or the direct effect of the drug on the lung or the pulmonary vascular bed. The changes are difficult to distinguish histologically from "uremic pneumonia." Perhaps with better control, we have had no deaths from this disease in two years. It has not been reported in patients taking pentolinium salts.

(3) Collagen disease may be caused by hydralazine. In about 10 per cent of patients a "collagen" disease simulating rheumatoid arthritis in its early stages and disseminated lupus erythematosus in its late stages is the result

usually of large doses of hydralazine taken for six to twenty-two months. Fortunately it is readily reversible when use of the drug is stopped; unfortunately diastolic normotension disappears within one month, and treatment by all the other agents at our disposal becomes only partially effective. The earliest sign, other than normotension, is a positive cephalin-cholesterol flocculation test. Any patient taking hydralazine and developing a painful or aching joint should be suspected of having "hydralazine disease."

(4) Fatalities due to substitution of placebos for potent drugs or to their discontinuation are common. Probably the least safe procedure in chemotherapy is discontinuation of drugs when the desired fall of blood pressure has been achieved. It is possible that the sudden rise of blood pressure accounts for the pulmonary edema or cerebral hemorrhage sometimes observed. Once committed to therapy, patients must be removed therefrom most cautiously and with full knowledge of the consequences.

OL.
1
955

Is it worth the effort? A procedure which will prolong life and prevent disability is worth the effort when the patient wishes to live. The effort involved in the control of severe hypertension is a little more time-consuming and considerably less complicated than is the effort expended by the patient for the control of his diabetes. For the physician, the effort and knowledge necessary are about equal for the two diseases.

In malignant stages, for the first month or so, patients often need encouragement to continue in the face of distressing side effect of ganglionic blockade caused by the large doses of drugs required. Death is the result of discontinuation. Mental depression, lassitude, and anorexia frequently accompany the fall of blood pressure; the period of adjustment appears roughly proportional to the severity of the disease. During this interval, neither patient nor physician can afford to become discouraged. The first two weeks of lowered blood pressure are usually the most arduous, for every day is a "bad day" for the patient. Soon the patient feels well for a day, followed by several "bad days." While the cause of these symptoms is not known, they are a function of the fall of pressure and not apparently of the action of any one drug.

In severe benign stages with secondary vascular disease, again the control of blood pressure appears to prolong life and prevent much of the disability associated with heart failure, cerebral hemorrhage, and possibly coronary arterial disease. Therefore, control is worth the effort, *provided that it is adequate.*

The gradual reduction in the amount of drugs necessary to achieve normotension is a gratifying sign that the underlying disease, in these two stages, is regressing. The unusual, but unequivocal cases where drugs can be discontinued for several months without rise in blood pressure, the more frequent cases where discontinuation of all but the least potent one (reserpine) maintains normotension, the numerous cases where small fractions of the original doses are necessary, and the examples where patients have passed physical examinations for life insurance or jobs suggest that the treatment is specific for vasospasm and therefore its consequences. Certainly this is worth the effort, as patients will attest.

There are grounds for disagreement on the control of milder stages of hypertension, i.e., in those patients whose blood pressure becomes normal under heavy sedation and, more especially, those whose blood pressure becomes normal with rest in bed. The ease of control with small doses of reserpine and hydralazine, with few or no side effects, and without the sphygmomanometric manipulations necessary for the use of ganglionic-blocking agents is some argument for therapy. Furthermore, one can make the safe prediction that the secondary, slowly progressive results of vasospasm will be prevented in the long run. On the other hand, it is true that a sizable proportion of older patients with moderate or mild hypertension will live a reasonable span of life without stroke, cardiac accident, or renal insufficiency. In these patients therapy is not worth the effort involved, unless it alleviates symptoms or slows the progress of atherosclerosis.

Since such individuals make up the majority of the hypertensive population, physicians are frequently faced with the decision, to treat or not to treat. Since such individuals are not insurable, it is probable that hypertension carries with it a risk to life. The matter really boils down to the questions: Are the drugs safe enough to use in mild and moderate stages? Can we predict accurately which patients are going to live out a normal lifespan with benign hypertension and which are going to die of cardiovascular diseases? Our own opinion based on experience is that the relatively small doses required for control of mild and moderate stages are quite safe to use for at least three years, especially since initial dosage levels can be reduced considerably after one year or more. Furthermore, we have these beliefs (while awaiting their disproof): (a) no one can choose accurately the patients who will become adjusted to hypertension and those who will not, (b) the secondary effects of the condition are usually progressive, although at various rates, (c) absence of hypertension is usually better than its presence, and (d) atherosclerosis is not a healthy state. Therefore, the conclusion is drawn that all patients with sustained hypertension, and most patients with fluctuating hypertension, should be treated in an attempt to achieve as normal a cardiovascular state as possible, provided that the patient wants to be treated. We recognize that a proportion are thus treated relatively needlessly. While it may take twenty years or more to determine the effect on mortality in these individuals, logic and reason demand normality in any disease which can be treated successfully. Even though the presently available drugs are only a stopgap, and the next twenty years, barring world cataclysm, will bring much more specific agents, hypertension need not now go uncontrolled, any more than did pernicious anemia with liver, syphilis with metals, or malaria with quinine. Prevention of early death and disability is the highest aim of medicine; one can reasonably expect to achieve this goal by controlling a chronic disease in its early stages before irreversible structural deformities occur, for then prevention of further damage is the best that one can hope for.

There is one other group of cases where controversy rightly exists, those exhibiting renal insufficiency. Lowering of the blood pressure in azotemic individuals can precipitate uremia. The choice of whether or not to treat, however, is by no means difficult when we realize what we are doing and what we are not doing. If we could assess the degree of renal vasospasm and the

amount of organic renal vascular obstruction it would be simpler; since we cannot, the only solution is to treat. The alternative to treatment of malignant azotemic hypertension is early death; with treatment life can be prolonged in most and indefinitely in many. When azotemia is advanced, however, the prognosis worsens, and in uremic states it is nil. It is our practice to treat uremic individuals by drugs when (a) hypertension is causing serious discomfort because of heart failure or cerebral edema, or (b) when azotemia lessens or remains stationary in the face of a moderately lowered blood pressure. Normotension, however, is usually inconsistent with unchanging renal function in these cases.

The degree of azotemia beyond which the situation is hopeless cannot be determined with accuracy. In our experience, nonprotein nitrogen values in blood of much more than 60 mg. per cent (by the Somogyi-zinc filtrate, which does not measure creatinine, uric acid, glutathione, and thioneine) carry a poor prognosis, although with patience and strict attention to dosages we have seen occasional recovery when levels were as high as 125 to 150 mg. per cent, and frequently no progression for many months at 100 mg. per cent. Strangely enough, the cause of the renal disease, whether it be glomerulonephritis, pyelonephritis, or other parenchymal disorder, does not apparently affect the result as long as severe hypertension existed prior to therapy. Frank uremia, from whatever cause, is intractable, although the comfort of the patient may be bettered by moderate lowering of blood pressure. In other words, the downhill course of the azotemic individual may be worsened, unaffected, halted, or bettered by treatment, which in any event requires extreme caution and close supervision.

To answer the question briefly, control of hypertension by drugs is certainly worth the effort in malignant and severe "benign" stages (which are no more benign than are congestive failure, coronary occlusion, cerebral vascular accident, dissecting aneurysm); it is certainly worth the effort in moderate azotemia and may be in more advanced renal insufficiency; it is only palliative in uremia and advanced azotemia; it may be worth the effort in moderate benign stages, especially when atherosclerosis is advancing; and the pros and cons must be weighed in milder stages. Since the potency of the drugs required is proportional to the severity of the disease (i.e., the vasospasm), an analogy exists with the treatment of diabetes; measures required for control increase in potency and exactness with the severity of the hyperglycemia. If all human hypertension were reversed to normotension, there would be no disability or mortality from its secondary effects.

What is the evidence? The recent literature is full of reports of cases treated with modern drugs with variable results. In fact, attempts are now being made to ascertain the relative potencies of two similar agents on the tacit assumption that both are effective but one may be a little more so. We have passed the stage where studies controlled by placebos are necessary. The evidence that any one agent or a combination of two or more will control hypertension, however, must be viewed critically by the following two criteria: (1) Mortality. It is safe to say that a procedure is certainly effective if it extends the life ***and***

lowers the blood pressure for one year or more in patients in accelerated malignant stages with azotemia, for two years or more in patients in malignant stages without azotemia, and for three years or more in patients with complications such as congestive failure and severe nephrosclerosis. Procedures are less certainly effective if they extend the life, lower the blood pressure, and prevent further cardiovascular complications for five years or more in patients who had suffered apoplectic strokes or coronary occlusion. Because effective neurosurgery is only seventeen years old and effective chemotherapy only three and one-half, Perera's statement that there is no convincing proof of any procedure extending the life of a patient in uncomplicated phases is true. Many of us, however, might question its eventual validity by pointing out small groups of sympathectomized individuals who appear perfectly normal in all respects but for the scars on their backs fifteen years later and who show no signs that they will die of hypertension during the next five.

(2) Blood pressure. Because many years must elapse before an effect on mortality of treated individuals in uncomplicated stages can be evaluated, sustained lowering of blood pressure and reversal of the secondary renal and cardiac findings is the only alternative criterion. This requires many measurements. It is not enough to give a potent but rapidly excreted drug, measure the blood pressure at the height of its action, and neglect the rebounds which invariably occur. Nor is it enough to give a patient a drug and measure his blood pressure at weekly or monthly intervals. Single readings are of little value unless changes are unequivocal, sustained, and fortified by clinical and laboratory findings. We have found it impossible to trust outpatient evaluations of ganglionic-blocking agents by monthly or weekly measurements of blood pressure, when we watch wide fluctuations occurring in the hospital at four-hour intervals. Our own data are based on 1,800 measurements a year, five a day, made by each patient or a member of his family, compared to six a day in the hospital, made by nurses every four hours including two during sleep. Only by extensive data can a drug be properly evaluated in terms of sustained control of blood pressure.

The evidence from our own series of patients is that sustained control by drugs can be achieved in cooperative individuals in all stages and phases of the disease except the severely azotemic, that mortality drops from 100 per cent to 21 per cent in the accelerated phase, from 36 per cent to 3.6 per cent in complicated stages, but that azotemia carries a 50 per cent risk.[1,2] These figures are based on twenty to forty-four months of treatment.

Why should I do it? This question has been answered indirectly in preceding sections; the answer should be obvious to any physician who expects more for his patient than the effects of "pills, powders, and promises." No treatment is perfect. Chemotherapy of hypertension is less perfect than some treatments for chronic diseases, but is better than many; it represents a calculated risk proportional to the severity of the disease. The ravages of the disease in its more severe forms are very risky to life and health. Naturally no treatment should carry risk of mortality; unfortunately many do. The one here considered, used properly, is less hazardous than many commonly accepted

VOL. 1 195

surgical and medical procedures using potent or drastic restorative forces. Most hypertensive patients prefer not to have hypertension; when the procedure is explained to them theirs is the ultimate choice. Perhaps the question should be phrased, "Why should I not do it?"

How can I do it? The technique of reducing and controlling hypertension with drugs is relatively easy. (a) Enough must be given to produce the effects desired without causing intolerable side effects. All drugs have side effects; the choice of blocking agent, for example, is a matter of the patient's preference and the physician's persistence. Adequate blood levels constantly maintained are essential. The rate of excretion of each drug must be recognized. (b) The cardinal rule of therapy is to lower blood pressure steadily and slowly. We have encountered few patients who could not tolerate two differently acting drugs when this was done. (c) The aim of therapy is sustained normotension; vagaries in absorption, utilization, and excretion of the drugs and in the condition of the patient make artificially established homeostasis in hypertension as variable as is artificially established homeostasis in diabetes mellitus. While a relatively flat curve of blood pressure is rarely attained at the outset of therapy, the mean pressure can be kept at normal or close to normal levels if desired and the mean deviation will seldom exceed 15 mm. and usually is less than 10 mm. Hg. When normal levels are not achieved at first (in severe stages) they often develop with time. (d) Knowledge of success or failure of therapy depends upon adequate data. The level of the blood pressure is the first criterion of successful treatment. It is not fair to our patients to use mortality statistics in determining whether or not a given regimen is effective; that stage of investigation has been passed. The blood pressure should be taken frequently, at least every four hours day and night, while it is being lowered. Evidence of effectiveness of therapy based upon single determinations made daily at a stated interval after a dose can be erroneous. We have many times demonstrated that excellent control was apparently achieved by use of a ganglionic-blocking agent when the blood pressure was measured three times a day; actually wide fluctuations were observed when measurements six times a day were made. (e) In our opinion, the use of a ganglionic-blocking agent by mouth requires self-measurement of blood pressure and self-determination of dosage according to prevailing levels, in order to avoid both hypertension and hypotension. We have been unable to devise any other method effective for providing even control. Reliance on symptoms alone to decide on the proper dose of one of the methonium compounds can give erroneous results; regularly recurring "spikes" of hypertension when the drug is excreted are usually asymptomatic. Postural hypotensive symptoms are caused by overdosage and have been used as a means of estimating maximal effective doses; recovery is often followed by hypertensive levels persisting until another dose acts. The range between asymptomatic normotension and hypertension can be as great as 120 mm. Hg or more when these short-acting and rapidly excreted drugs are used. Therefore, we are unable to trust control of blood pressure with erratically absorbed ganglionic-blocking agents in emotionally unstable individuals to any other means than the sphygmomanometric. Parenthetically it can be fairly stated that no fear

or anxiety attends self-measurement when the patient discovers that a dose will bring the blood pressure down; lack of effect, however, may cause further elevation. (f) Patience, persistence, and optimism are essential prerequisites for the physician. Half-hearted, skeptical trials with insufficient doses are of no value. We have observed many patients continue a downhill course into uremia while taking insufficient doses of potent agents or large doses of impotent ones. (g) Doses of one agent should be altered daily until the desired effect is achieved. Tolerance to all agents develops; it can be avoided by persistent and even pharmacologic pressure. The only resistant cases we have seen were in patients who received intermittent therapy. The second attempt to lower blood pressure is much more difficult than is the first.

Many methods have been advocated. Naturally, we prefer our own[3-5] because of our inability to modify it and achieve the desired results. Once established for one or two months, a patient need be seen only at infrequent (three- to six-month) intervals, provided he keeps records. The final aim of therapy is to return a patient to a useful life (within the limits imposed by prior irreversible damage to brain or heart). When this aim is not reached and reached early, therapy has failed.

VOL. 1 1955

Other forms of therapy are by no means obsolete in selected cases. Surgical sympathectomy has its use in patients who cannot, will not, or prefer not to use drugs. Dietary salt restriction is unnecessary in most cases, but may serve as an adjunctive measure for those unable to take hydralazine or for the first few months of congestive heart failure on therapy. The drugs, however, have extended the range of successful treatment far beyond that attained with other measures.

Perera has posed five significant questions. *Is the level of the blood pressure a major factor in the development of the complicating pathologic changes?* Within the bounds of present knowledge, the answer can be an unequivocal affirmative, if one includes the biochemical abnormalities upon which hypertension is dependent. All the common secondary changes, cardiac hypertrophy, dilatation, and failure, arteriolar nephrosclerosis, and that portion of the atherosclerotic process influenced by high intra-arterial pressure, can be considered dependent upon physical or chemical factors. The contrary evidence forms exceptions to this general rule; occasionally complications develop late in a course, there is a lack of correlation between the effects of sympathectomy (admittedly an incomplete therapeutic procedure in one-half of patients) and other hypertensive manifestations, and occasionally pathologic changes progress after the blood pressure has been "unphysiologically" or even "physiologically" lowered. No dynamic or chronic disease process is the same in every individual.

Are the peaks of elevation more harmful than the resting level? The answer is equivocal. Certainly the mean yearly pressure might influence the total yearly work of the heart; cerebral hemorrhages and even thromboses may occur with emotional stress and presumably "spikes" of pressure. There are no data, however, bearing on this influence on the nephrosclerotic process. We have often wondered, as have others, whether the favorable effect of surgical sympathectomy in patients who sustained no change in supine levels may not be the

result of the postural fall associated with the sitting or standing position in which two-thirds of the time is spent.

Does the accelerated phase represent only a quantitative increase in the tempo of the disease? The answer is not known. Clinical impressions suggest, however, that "something new has been added" in the role of the kidney, almost as though the renal vasospastic mechanism and its controls had become "decompensated." The relief of vasospasm, however, reverses the process unless it is far advanced, but understanding of how and wherefore is deficient. This phase is, however, especially common when the kidneys are already the seat of disease.

Are the mechanisms which produce retinopathy identical with those which produce nephrosclerosis and renal damage? The answer is not apparent, although the two processes may be closely associated. From a consideration of the anatomy of the retinal vessels (thin-walled, weakly muscular structures) one suspects that *lack* of vasoconstriction of a degree equal to that of the remainder or the vascular system produces capillary engorgement, exudation of fluid and protein, hemorrhage, and possibly papilledema. A similar process, *lack* of adequate constriction of diseased renal vessels with severe hypertension, may account for the "flea-bitten" kidney. Thus the retinal changes may be merely a manifestation of a high diastolic pressure secondary to other decompensated renal mechanisms. They disappear rapidly when the pressure is lowered by drugs.

The fifth question can be answered positively. *Does control of hypertension stabilize or reverse the basic process? Or does the underlying disease advance inexorably in some esoteric manner in spite of a lowered blood pressure?* We have little understanding of the basic disease other than that part which is influenced by drugs; we have poor means of measuring what is altered biochemically and physiologically. By the rough clinical measurements at our disposal, however, the question can be answered for most patients categorically when control is good. Renally, proteinuria disappears, concentrating ability increases, and the ability to excrete injected phenol red rises. Renal plasma flow probably increases. These changes are progressive during several years. Many formerly damaged kidneys become normal according to established clinical standards. Heart size diminishes, electrocardiographic abnormalities dependent upon strain regress, and many hearts become normal according to established clinical standards. Evidences of myocardial infarction do not usually change. These alterations require two years or more for completion—and they are not universal. Cerebral hemorrhages do not occur in our experience and thromboses are unusual in patients having previously suffered one or two attacks. Ocular fundi revert to normal, hard exudates slowly absorb, spasm disappears, and even tortuosity may regress. Symptomatically, patients are well. Physiologically, the response to exercise—and even the Schneider index—may be normal (perhaps a false normal through ganglionic blockage). Pupils react, bowel function returns, sweating reappears. Until we have very delicate methods for detecting the basic abnormality in the disease, we will not know whether modern drug therapy causes a reversal to normality or merely causes further abnormality which masks the disease and its progression. There is no evidence whatsoever at the present

time that adequate control of hypertension by drugs does *not* reverse the underlying process, whatever it may be. When our measurements, particularly of renal function in azotemic individuals, do not alter favorably, at least we have seldom seen them worsen. Naturally enough, drugs will not dissolve scar tissue.

If there is a common denominator between hypertension and atherosclerosis, is that affected favorably? We do not know. The only vaguely suggestive evidence that it may be lies in the almost invariable fall of plasma cholesterol induced by hydralazine. All elevated levels have dropped to normal in our patients, some to low normal values.*

The answer to the first and last question, "What do I do about hypertension?" is clear. You lower the blood pressure to normal and keep it there indefinitely day and night. When you believe or discover that a normal blood pressure is inconsistent with nitrogen balance in azotemic patients, or with local cerebral or coronary blood flow in atherosclerotic patients, you compromise. When you cannot keep it normal with large doses of drugs you get it as low as you can and wait for a more gradual change.

The drugs you have available are potent and effective but imperfect. You must avoid serious side effects (which are usually the result of a primary action of the drug) before they occur. You must alter long-established abnormal hemodynamics slowly to avoid local vascular occlusion or insufficiency. You must understand hypertension, at least in its pathologic physiology, and you must know where your drugs act, and if knowable, how. You must be familiar with late toxic reactions, and reduce doses to avoid them. You can meanwhile wait for new and better agents. Above all, you must give your patient the benefits of modern therapeutic methods, in order that he may avoid irreversible vascular changes, and not chance delays if his condition is serious.

Since malignant hypertension is no longer the uniformly fatal disease that it has been in the past, and other less serious forms can be partly or completely controlled, the burden of decision on a physician is no longer "Can I treat?" but "How vigorously shall I treat?" Untreated patients nowadays are a grave responsibility. Let us hope, however, that the next ten years will see the obsolesence of present methods of therapy, which are merely a first, although successful, approximation of the ideal.

Appendix

General Considerations Relative to Chemotherapy

A. *Rationale.*—In all but the mildest cases of intermittent hypertension, in which neurogenic influences are believed to be the principal factor causing vasospasm, the combination of a procedure or drug acting on autonomic nerves and one acting on vascular smooth muscle is necessary for even control of blood pressure at normotensive or near normotensive levels. The potency, dosage, or thoroughness of each must vary directly with the severity of the generalized vasospasm

*Another less objective indication is the frequent voluntary statement of atherosclerotic patients that lower and lower levels of blood pressure could be tolerated without symptoms year after year; if 150 mm. systolic caused distress at first, for example, in two years similar distress did not appear until 110 or even 90 mm. Hg was reached.

and the proportion which each influence, neurogenic and muscular, contributes to the total. In general, the neurogenic influence may be estimated by the sodium amytal test or the injection of tetraethyl ammonium chloride; if the blood pressure falls to low normal levels, drugs or procedures acting on autonomic nerves can be expected to be more successful than when it remains high (sizable smooth muscular or nephrogenic influence).

B. *Choice of Drug or Procedure.*—Cases may be roughly classified according to the stage of hypertensive vascular disease, with greatest attention being paid to the severity of the vasospasm and least to secondary complications of atherosclerosis. This attitude is important, as vasospasm, and not vascular disease, is being treated.

Stage I comprises patients with elevated levels of blood pressure during a physician's examination but normal or lower levels part of the time, corresponding to early stages of Perera's "uncomplicated asymptomatic phase." Admission to hospital and frequent measurements by nurses combined with diagnostic procedures under the heavy hand of the house officer lower it to normal, often dramatically. Reserpine will effectively control about one-half of these cases; in the remainder small doses of hydralazine (75 to 200 mg. per day) may be necessary. We do not advocate the use of protoveratrine or available blocking agents in these individuals, for their irregularity and intermittency of action may cause hypotensive symptoms. A very long-acting ganglionic-blocking agent, however, should be effective.

Stage II comprises patients with elevated levels of blood pressure at all times except during heavy sedation (sodium amytal). It corresponds partly to Perera's "symptomatic uncomplicated phase" and partly to his "complicated phase."* Serious secondary atherosclerotic complications may or may not be present; if so, about 30 to 40 per cent may be dead in three years. Reserpine plus fairly large doses of hydralazine (300 to 400 mg. per day) will control about one-half of these cases eventually; the remainder will require the addition of ganglionic blockade. With time, individuals in this stage uniformly exhibit reversal of the process and marked reduction of dosage; in two to three years a majority can be maintained on reserpine alone and a few will be in a complete but possibly temporary remission.

Stage III is made up of individuals with Grade II to III (Keith-Wagener) ocular fundi with or without occasional hemorrhagic and exudative lesions, with severe generalized vasospasm and hypertension not relieved by heavy sedation (sodium amytal). Renal function is adequate but usually reduced. Serious atherosclerotic complications may or may not be present. In this stage, which usually carries a poor prognosis (40 per cent dead in three years), ganglionic blockade plus adequate doses of hydralazine (500 mg. or more per day) is essential for control. Reserpine may be added or not, mainly for its sedative action in smoothing out variations in blood pressure caused apparently by emotional lability in the presence of incomplete and irregular ganglionic blockade. Therapeutic results are good, 95 per cent surviving three years, with considerable eventual reduction in dosages in most.

Stage IV corresponds to Perera's "accelerated phase," or what is commonly called "malignant stages." For therapeutic purposes it can be divided into three substages, (a) early, in which hemorrhagic and exudative retinitis is present but not marked (Grade III to IV) and renal function is reduced but adequate, (b) severe, in which retinitis is advanced and renal function is borderline, and (c) azotemic, in which nitrogen retention has occurred. Each substage carries a different prognosis, three-year survivals of treated patients being roughly 100 per cent for (a), 80 per cent for (b), and 50 per cent for (c) without frank uremia. Ganglionic blockade plus

*It will be obvious to the reader that the degree of lability of the vasospasm is the factor which determines these stages. Complications such as cerebral vascular accident and coronary arterial occlusion can occur in any stage, mild, severe, or normotensive, as they are caused not directly by vasospasm but by an associated disease, atherosclerosis. The fact that this other disease can be influenced by the severity of the hypertension, i.e., the vasospasm, has little to do with therapeutic measures aimed at vasospasm. Therefore, Perera's classification, as well as Smithwick's, is valid for other purposes than the choice of drugs or procedures, the former being prognostic and the latter prognostic and for surgical risk. One would not use the most potent drugs in a patient with hemiplegia or congestive heart failure who exhibited severe atherosclerosis and mild hypertension; one would use them, however, in a patient with severe but asymptomatic diastolic hypertension and retinitis without serious cardiovascular damage having yet occurred.

adequate doses of hydralazine (500 to 1,000 mg. per day) is essential for reversal of the stage. In general, control of hypertension is easier to achieve and is more even than with patients in Stage III; reduction of dosage is the rule after six to twelve months except in azotemic individuals. The systolic pressure can usually be maintained at or near former diastolic levels.

C. *Alternative Procedures When a Drug Is Not Tolerated.*—All the drugs—and procedures—carry risks of serious side actions in a small proportion of individuals. Since discontinuation of one of the two potent agents in severe hypertension carries a hazard of death from hypertensive causes, alternative measures, usually more drastic or compromising than the drugs, must be utilized to keep the blood pressure low.

Hypothalamic "blockade" by reserpine: Reduction in dosage will often alleviate the usual depressive effects of the agent and may reduce the number of nightmares, but abnormal reactions, such as anxiety, restlessness, nervousness, insomnia, emotional tension, and paranoid depression, require discontinuation; the last may disappear very slowly. Epistaxis induced by the drug usually necessitates discontinuation. The time-tested sedatives are the only alternatives.

We have seen three patients whose severe hypertension was "cured" for several months in that all drugs but reserpine were slowly discontinued during two to three years. One became ill with symptoms and findings of duodenal ulcer, in another ulcer became severe with massive hemorrhage and perforation into the pancreas, requiring partial gastrectomy, and in the third serious mucous colitis and proctitis with ulceration and bleeding was discovered. Because reserpine produces relative parasympathetic overactivity, it was believed to be contraindicated in these individuals, and complications such as these are being watched for in other patients.*

Ganglionic blockade by methonium compounds: Partial organic obstruction to a hollow organ, particularly the gastrointestinal tract, may become complete or subtotal by reason of parasympatholysis. When the drugs cannot be tolerated, protoveratrine can be substituted with good results. Surgical sympathectomy, of course, does not carry this hazard. Partial prostatic obstruction may require surgery.

Intolerance to hydralazine: High fever, aching, and malaise appearing during the first few weeks of administration of hydralazine require discontinuation or marked reduction of dosage. Fortunately such sensitive individuals are rare. Angina pectoris can be made worse (or relieved) by hydralazine. A compromise partial control of hypertension by neurogenically acting drugs plus, perhaps, restriction of dietary sodium may provide some measure of vascular safety, which, while not ideal, may lengthen life. In our experience, patients with *severe* hypertension are rarely intolerant to this agent.

Hydralazine disease appearing after six to twenty-four months of ingestion of fairly large doses necessitates two courses. Stopping the offending agent entirely results in return of hypertension; in these patients the mortality rate from hypertensive causes is 10 per cent. Large doses of ganglionic and hypothalamic blocking agents with or without protoveratrine usually fail to control the hypertension adequately; wide swings from high to low levels take place daily. This situation is about the most difficult to meet in therapy and we have no solution. Low-salt diets or thiocyanate might be used; sodium azide has been valueless. Closely related analogues of hydralazine have caused recurrences of the disease and chemically less related ones have been relatively worthless.

The second choice involves marked reduction of the dose and the possible addition of cobalt chloride (50 mg. per day orally) for one month and perhaps pyridoxine or cortisone until symptoms subside. The disease resembles a phenomenon of depletion; although we do not know what has been depleted, intelligent guesses can be made (Table I). While blood pressure can be controlled by small doses, "L-E" preparations may remain positive, the disease remain in a subclinical

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***These developments stimulate speculation. If psychosomatic influences are blocked in one somatic nervous pathway, the sympathetic, perhaps excessive outflow through the other, the parasympathetic, has led to gastrointestinal disorders. The patient is determined to develop a psychosomatic disease; when we do not allow him (or usually her) to have one kind, he gets another. Reserpine may or may not be an etiological agent.**

"lupoid" stage, and the patient's situation be potentially precarious. Discovery of a substitute for hydralazine which will not cause this phenomenon is the only real solution to the problem.

Hazards of severe restriction of dietary salt are well known. The nephrosclerotic kidney is a "salt-losing" kidney to some extent, and hyponatremia with renal failure (the low-salt syndrome) can be induced by limiting the intake to a point less than obligatory urinary losses. Borderline renal function predisposes to this usually fatal condition.

D. *Tolerance to the Action of Drugs.*—No tolerance seems to develop when both types of drugs are used correctly and continuously. On the other hand, tolerance is common when therapy is intermittent, an unexplained phenomenon.*

One of the most difficult situations to meet is in the patient whose blood pressure has been lowered successfully, only to have the drugs discontinued because of undue alarm at side effects or the consequences of normotension (mental depression, malaise, lassitude, weakness). The hypertension which recurs immediately is much more resistant to therapy and requires much larger doses of drugs after a few days than it did initially; sometimes it seems impossible to treat. We have encountered no resistance in "fresh" untreated cases; the secret of successful therapy is continuous therapeutic pressure. While we cannot account for this phenomenon, it is commonly observed and hazardous to the patient. Too many lives have been lost by "nervous" and erratic therapy.

OL.
1
955

E. *Details of Method for Severe Hypertension Treated First in Hospital.*—Specific details of the methods which we have found effective in controlling almost all cases of severe hypertension, with instructions to the patient and the nursing staff, have been published.[5] The cardinal principle is to change hemodynamics *slowly*. They may be briefly summarized:

1. Blood pressure is measured by competent nurses every four hours day and night, and charted. More frequent measurements are essential in hypertensive emergencies when parenteral administration of drugs is necessary After the three or four days required for evaluation of the stage of the disease and the status of kidneys, heart, blood vessels, and lability of blood pressure, a ganglionic-blocking agent is begun in small doses at four-hour intervals day and night. Reserpine (1.0 mg. once a day) is usually given to those in Stage III.

2. The choice of the agent is a matter of individual preference. Hexamethonium chloride is a time-tested and predictable drug. Side effects may be severe with large amounts. The initial dose is usually 125 mg. every four hours for the first day, increasing by 125 mg. increments per dose daily until repeated swings to normotension are seen or 500 mg. per dose is reached. Pentolinium bitartrate is approximately five times as potent; therefore 20 mg. is the initial four-hour dose, increasing daily to 40, 80, and 100 mg. per dose. In our experience, relatively larger amounts of pentolinium salts can be tolerated without intractable parasympatholytic symptoms,† but in many individuals control is less even and "smooth" and wide fluctuations may occur. Each "dip" in systolic pressure gives the physician confidence in the lowest levels tolerable without cardiovascular accident.

3. Routine orders before reaching the final amount of blocking agent include (a) omission of the dose if the systolic pressure at the time is below a certain level, usually 140 mm. Hg (slightly higher "omit" levels are used in atherosclerotic and azotemic patients), and (b) a nightly laxative with citrate of magnesia daily if there is no bowel movement before noon, in order to avoid obstipation before it occurs. After the full dose is reached (in four days) the orders are written in

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***This is reminiscent of the battle between Hercules and the giant Anteus, son of Earth; each time the giant was thrown to his mother Earth, he arose seven times stronger to continue the fight. After many falls, even the mighty Hercules became weary. Only by lifting him high and strangling him was Hercules able to kill the giant.**

†One patient formerly in malignant stages is taking 4.0 Gm. pentolinium bitartrate per day in five doses, an amount which corresponds to 20.0 Gm. of hexamethonium salts. Few individuals can tolerate 5.0 Gm. of hexamethonium chloride a day in divided doses. On the other hand, in a number of patients analyzed, the mean systolic deviation was twice as great with pentolinium as with hexamethonium salts whether or not hydralazine was added.

such a way that the patient receives it at each four-hour interval if the systolic pressure is over 140 mm., one-half the dose if between 140 and 130, one-quarter the dose if between 130 and 120, and none if below 120 mm. Hg in the supine position. By this time the blood pressure is either fluctuating widely* or little pronounced effect is evident; normotension is not sustained.

4. Hydralazine is then begun at 25 mg. every four hours, increasing daily by 25 mg. per dose until 100 mg. is reached. Hydralazine is given regardless of the level of blood pressure. It disappears rapidly from the blood. At the end of this four-day period the patient and his record are evaluated; if relative normotension is not maintained and fluctuations of pressure are less marked, the dose of one or the other agent is adjusted upward until results are satisfactory. Maximal (but unusual) single doses of hydralazine can be as high as 200 mg.; of hexamethonium chloride 1.0 Gm., of pentolinium bitartrate 300 mg. or more.

5. Before discharge, measurement of blood pressure is made with the patient seated, the amount of ganglionic-blocking agent automatically adjusting itself as postural effects occur. One dose of both agents in the middle of the night is omitted; the usual result is a rise in the morning "resting" or "basal" pressure. The patient is taught to take his own blood pressure five times a day before each dose and record it on special charts. He is instructed on the actions of the drugs and their side effects. He leaves the hospital on the same schedule, which was designed to prevent both hypertension and hypotension. By keeping a daily record, trends can be observed which are invaluable for efficient therapy. In our clinic, we examine a patient one month after discharge from hospital, and then at three- to six-month intervals if he is doing well. Patients seldom complain of the inconvenience, which takes about fifteen minutes a day, but they do object to the cost, which now runs from $20 to $30 a month without reserpine (an extra $4.50).

6. If the dose of the ganglionic-blocking agent automatically falls to negligible quantities (in six to eighteen months) by reason of sustained normotension, the dose of hydralazine is then reduced to four times a day, three times a day, twice a day, and finally halved at two- to six-month intervals. Reduction in dosage is made very slowly. The amount of reserpine is halved in one or two months if drowsiness appears, and then halved again until symptoms disappear.

7. In hypertensive crises (pulmonary edema, cerebral edema) requiring parenteral administration, two lines 20 mm. apart are drawn across the graphic chart at the level at which systolic pressure is to be maintained. After initial lowering of blood pressure by a small dose of a blocking agent, blood pressure is measured every hour and a subcutaneous injection of the full effective dose given if it is above the upper line, one-half the dose if between the lines, and none if below the bottom line. Changes in total dosage must be made often. The second day the two lines are drawn 20 mm. lower. Thus, a patient with encephalopathy (wet brain) may have his pressure reduced from 300 mm. Hg to 220 to 200 mm. the first day, 200 to 180 mm. the second day, and 180 to 160 mm. the third day. Usually oral medication becomes possible long before this time. The pressure must be reduced more drastically when there is pulmonary edema. We prefer parenteral ganglionic-blocking agents to parenteral hydralazine because of their shorter actions with less tendency to produce prolonged hypotension.

F. *What to Do if a Patient Is Not Doing Well.*—The patients who do least well on combined therapy are usually men in the sixth decade with atherosclerosis, and not, as might be expected, those in malignant stages. Certain individuals, however, because of too early reduction in dosage or because of a dosage schedule sufficient for the hospital but insufficient for the stresses of active living, continually show hypertensive levels, reaching as high as 180 or even 200 mm. Hg systolic during one of the five measurements a day. Several choices are open. (a) The dose of one agent is increased for one month. If not successful, the dose of the other agent is increased. (b) Protoveratrine in amounts insufficient to cause nausea is begun. (c) Dietary salt is restricted moderately. (d) Cobalt chloride is added for one month or more. (e) The patient is readmitted to

*The available agents given orally have roughly a four-hour effect. Pentolinium salts are supposed to act a bit longer, but in most patients they do not. Effects are most variable, however. In one individual, for example, not taking hydralazine but taking pentolinium bitartrate every eight hours, a consistent sharp *rise* in blood pressure occurs four hours after a dose with a fall at eight hours; in his case the full dose is taken when the pressure is low. His extremes of fluctuation during a two-week period are usually between 240 and 80 mm. Hg systolic.

the hospital and restabilized. (f) Pheochromocytoma is suspected in patients whose blood pressures fluctuate wildly and cannot be controlled. Reduction in dosage is not possible for those who keep themselves moderately hypertensive, even after three years. Those who do best are those who attain and maintain normotension.

REFERENCES

1. Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. V. Effects on the Course of the Malignant Stage, Circulation **10**:321, 1954.
2. Schroeder, H. A.: Management of Arterial Hypertension, Am. J. Med. **17**:540, 1954.
3. Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. I. Effect on Blood Pressure, Circulation **8**:672, 1953.
4. Schroeder, H. A., and Morrow, J. D.: The Control of Arterial Hypertension by Hyphex, M. Clin. North America **37**:991, 1953.
5. Schroeder, H. A.: Hypertensive Diseases—Causes and Control, Philadelphia, 1953, Lea & Febiger.

OL.
955

TREATMENT OF HYPERTENSION

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1
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IN A conventional paper the tendency is to confine subject matter to topics on which adequate information is available. There are questions such as those raised by Dr. Perera, and others which arise from time to time in panel discussions, which are not confined to headings commonly introduced in formal articles. Nor are exact studies available on all the matters with which they are concerned. We are encouraged by Dr. Perera's introduction to attempt direct replies to questions which have arisen in panel discussions and clinical meetings and in letters which we have received from doctors relating to the care of hypertensive patients. It may be assumed that the answers to questions represent views held in common by most members of our clinical group here. This presentation takes the form of a synthetic panel discussion in which the panel members are designated as P. M. We have introduced into our imaginary audience at least some doctors whose views are not entirely in accord with our own.

Dr. A.: I have a few hypertensive problems lined up which I would like your advice about. The first is the very frequent one of whether or not to start active treatment on a particular patient. This one is a woman of 64 years, well preserved, very active, and in excellent health up to this past twelve months—since when she has complained of headaches. On physical examination I cannot find much wrong with her except that she has quite a substantial degree of hypertension, usually running about 220/110 when she comes to see me. Should she have active treatment for it or not?

P. M.: I think we must have some more data before attempting to answer that. You say the physical examination was negative. Did you examine the fundi?

Dr. A.: Yes. There was some variation in the caliber of the vessels and a-v nipping, but the discs were normal and there were no hemorrhages or exudates.

P. M.: Grade II, in fact. Did you have her chest x-rayed?

Dr. A.: Yes. The heart was little, if at all, enlarged and the lung fields were clear. The electrocardiogram was virtually normal too.

P. M.: The urine?

Dr. A.: Normal.

P. M.: Have you had any other investigations done?

Dr. A.: No.

P. M.: There are one or two others I like to have done as a routine; in particular, the "basal blood pressure." This is intended to demonstrate the lowest level to which the blood pressure will fall with the patient fully sedated. The patient is admitted to the hospital the evening before and is given 0.2 Gm. of pentobarbitone. This is repeated at 7 A.M. unless the patient is unusually small or frail, in which case 0.1 Gm. is given. The patient remains in bed. At 9 A.M. a technician takes a series of blood pressure readings at intervals of one minute for fifteen minutes. The lowest of these is taken as the "basal blood pressure." The idea of a series of readings is to eliminate the effect of the nervousness which might be induced by the taking of the blood pressure.

If the patient you describe has a low basal blood pressure, say about 130/90, probably indicating a reasonably low blood pressure during sleep or even during the day when not under observation, her prognosis without treatment may even be as good as it is with treatment. However, a basal blood pressure of 175/100 or more is probably an indication for treatment even in a symptomless patient.

Dr. B.: Do you not place any weight on "casual" readings at all?

P. M.: Oh, yes indeed, and I would say that repeated casual blood pressure readings of 230/120 or more constitute an indication for treatment.

Dr. C.: What other features would you say made treatment necessary? In any patient I mean, not this particular one.

P. M.: Congestive cardiac failure, cardiac asthma, encephalopathic attacks, and the finding of severe hypertensive changes in the retinas—hemorrhages and exudates and of course papilledema—are unequivocal indications for treatment. Exertional dyspnea with cardiac enlargement due to the hypertension and electrocardiographic evidence of hypertensive strain are also strong indications for treatment. Headache, dizziness, "black-outs," and so on have to be assessed on their merits. Headache is particularly hard to evaluate. Sometimes only a trial of treatment will decide. Moderate hypertension in an earlier age group and particularly in males is sometimes of ominous import, calling for treatment.

Dr. A.: Is her age any bar to treatment?

P. M.: Not 64. In patients over the age of 70 hypotensive drugs have to be handled carefully, but if the indications for treatment exist there is no reason why they should not get it. As for your fear of a stroke, it is a little difficult to be certain that treatment, as it has been available up to the moment, does in fact lessen the frequency of strokes. We have lost Grade II and III patients, mainly older ones, who were otherwise doing very well, from cerebrovascular accidents. But we hope that the regimen we are using now for many of our severe hypertensives, namely, reserpine and pentapyrrolidinium in combination, may cut down the incidence. For those of you who do not know that name, pentapyrrolidinium is also known as pentolinium and Ansolysen.

Dr. C.: Does a previous cerebral vascular accident contraindicate treatment?

P. M.: No; but as a matter of policy we usually wait six weeks after a cerebral thrombosis before starting. Or for that matter after a coronary.

Dr. B.: Coronary artery disease, then, does not preclude treatment?

P. M.: No. Relief of anginal pain occurs in many patients when adequate control of blood pressure is established. Some patients get pain if the pressure falls fully to normal and in these patients and also those with symptoms of cerebral ischemia we aim at a somewhat lower fall of blood pressure at its lowest point, say to 140 systolic rather than 120.

Dr. D.: Do the therapeutic indications you listed for essential hypertension still hold for hypertension secondary to, for instance, unilateral kidney disease?

P. M.: In so far as a hypertensive problem may remain after consideration has been given to the underlying problem, yes. In cases where hypertension is a physical sign of a recognizable and potentially remediable primary disorder such as unilateral kidney disease or Cushing's syndrome, or coarctation of the aorta, or pheochromocytoma, then treatment of the underlying condition obviously takes first place. Incidentally, the possibility of one of these must always be well forward in one's mind. But in other circumstances, as in the hypertension following toxemia of pregnancy, or in chronic nephritis, there is no effective treatment for the primary disorder and treatment can be directed only against the secondary hypertension, just as in the poorly understood disease we know as essential hypertension. Hypertension, primary or secondary, becomes itself a cause of a number of symptoms, objective clinical manifestations, and pathologic changes. There is now strong evidence that if blood pressure reduction is maintained for a sufficient part of the twenty-four-hour day it leads to a considerable amelioration, often to the disappearance, of the various reversible clinical manifestations which we describe as hypertensive. This disappearance does not depend upon the nature of the original pathologic process which led to the high blood pressure, nor to an important extent upon the means used to reduce the blood pressure—so long as, in the particular patient concerned, they are effective.

Dr. E.: Is impaired renal excretory capacity a point against treatment?

P. M.: No. Persons with chronic nephritis respond well as far as those manifestations of their illness which are due to hypertension, but the prognosis is very much worse than in cases with normal renal function. It seems that the process in the kidney is likely to take its course independent of the extent to which the hypertension is ameliorated. It is as well to have a test of renal function done before starting treatment if practicable and to watch that blood pressure reduction does not lead to nitrogen retention. Actually it seldom does.

Dr. F.: Leaving nephritis aside, just what can be hoped for in really severe cases of essential hypertension or, for that matter, ma-

VOL. 1 195

lignant cases? I sent a man into your ward three or four weeks ago with malignant hypertension. He had papilledema, hemorrhages, and exudates, gallop rhythm, and a blood pressure of 240/170. He was only 42. He came along after a bout of paroxysmal nocturnal dyspnea.

P. M.: Yes, I remember him. He is doing alright. His papilledema has lessened but it may not disappear entirely for six months or more. The hemorrhages are disappearing but the star-shaped figures at the maculae may persist for twelve months. Incidentally, his cardiac manifestations have settled down quite well on the hypotensive therapy alone, without digitalis or salt restriction, and so forth. This is usual in younger people with high pressures who are placed on an effective regimen, but benefit is of course much less certain in elderly patients who go into failure with moderate hypertension. Not infrequently there is improvement in heart size and in the electrocardiographic picture. With effective treatment severe hypertensives are more likely to show decrease rather than further increase in heart size.

Dr. E.: What about actual life expectancy?

P. M.: The clinical improvement in patients with hypertensive heart failure suggests strongly that life has been extended in these patients. In our series of malignant hypertensives life has been prolonged to a statistically significant degree. This has also been reported by others. Furthermore, most of the men and women who were not permanently disabled before treatment started and who untreated would not be expected to have survived are leading productive lives. The good results are obtained mainly in patients with a blood nonprotein nitrogen under 60 mg. per cent. It is harder to be sure with patients of Grades III, II, and I, as the improvement seen in our figures is not statistically significant.

Dr. A.: You seem to agree we ought to treat my patient of 64. How would you start her off?

P. M.: There is no urgency about treatment in this case, and I would start her on reserpine, adding a ganglion-blocking agent later if necessary. Of the reserpine I suggest 0.5 mg. three times a day for one week, and thereafter 0.25 mg. twice or thrice daily, depending on side effects. It is likely to be a fortnight before the effect on the blood pressure is well developed.

Dr. D.: In what proportion of cases is reserpine alone effective?

P. M.: In our experience about one in four have falls outside the placebo range and most of these are relatively mild ones in whom the basal blood pressure is low. However, the fact that the blood pressure is reduced below the basal blood pressure in these indicates that it is having a true hypotensive effect. Moreover, just a few of the patients who have reacted have been among our more severe ones with high basal pressures and objective clinical manifestations. Reserpine alone is never adequate for control of malignant hypertension or congestive cardiac failure. We always start treatment with a ganglion-blocking agent in such cases and perhaps add reserpine later.

Dr. E.: How does reserpine act?

P. M.: It seems to diminish vasomotor pressor reactivity by a central effect on the nervous system, but it also probably has some direct vasodilating effect on blood vessels.

Dr. B.: Does reserpine have any side effects?

P. M.: With doses of the order of those I suggested for Dr. A's patient, namely, 0.5 to 0.75 mg. a day, side effects will not usually be important. The principal ones, when they occur, consist in flushing of the face and injection of the conjunctivae, congestive nasal obstruction, sensations of fatigue, sleepiness during the day often with lack of sleep at night or nightmares, shivering, and occasionally restlessness. Easily the most serious effect we have encountered has been mental depression. It has occurred in about 8 per cent of cases. Most of our patients who became depressed gave histories of previous episodes of depression and a previous history of this may be taken as a contraindication to the use of reserpine. Patients almost always gain weight, at times excessively. Dr. Perera's finding of sodium retention may in part be the explanation, although there is frequently a considerable increase in appetite. At times reserpine seems to precipitate biliary colic in patients with gallstones and also bronchial asthma in those subject to it.

Dr. A.: If after a fortnight's trial the blood pressure has not been adequately controlled by reserpine alone you suggest a ganglion-blocking agent as well?

P. M.: Yes, and my choice at the moment is pentapyrrolidinium. It is a methonium compound and resembles hexamethonium closely in its action except that it has a longer period of action and is about five times as strong. The great advantage is that it can be given successfully by mouth in the majority of patients.

Dr. C.: How much would a patient like Dr. F's need?

P. M.: The dose must be determined by the individual response of the patient. There is only the broadest correlation between the severity of the manifestations and the dose required for full effect. The dose to be discovered when using methonium compounds is that which brings the systolic blood pressure measured in the standing position down to 120 mm. Hg at the trough of the blood pressure fall. The securing of this degree of blood pressure reduction is, we believe, the key to success with methonium salts. It involves, however, a fine adjustment of the dose. Smaller doses aiming at modest falls, say, 160 systolic at the trough of the blood pressure fall, usually fail, because the duration of fall may be reduced even more than the extent of the fall. It must be emphasized that the achievement of a fall of adequate duration depends on reduction of blood pressure to an adequate degree.

Dr. X.: How do you manage to achieve your "adequate degree of blood pressure reduction"? I found when I tried hexamethonium that if I succeeded in reducing their blood pressure at all they would pass out.

P. M.: May I respectfully suggest, sir, that satisfactory management rests upon a considerably more meticulous attention to dose and effect

than is generally regarded as necessary in drug therapy. The treatment of patients with the methonium compounds is for all practical purposes an individual bio-assay—one "titrates" the dose accurately and under standard conditions so as to induce a certain desired effect. With a dosage scheme designed for the individual patient it is possible in most patients to get a good control over blood pressure levels with comparatively few side effects. Pentapyrrolidinium is, of course, superior to hexamethonium in that the slope of the sides of the trough is more gradual. Fig. 1 shows the time relationships of the blood pressure fall with ideal doses of hexamethonium and pentapyrrolidinium.

Dr. B.: But is not postural hypotension a serious side effect of treatment with the methonium compounds?

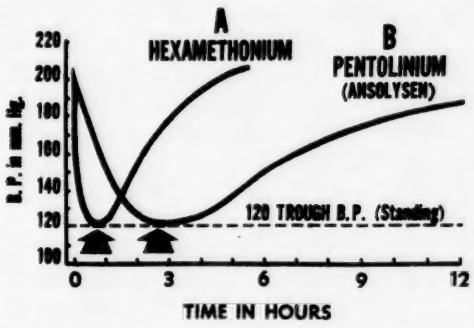

Fig. 1.

P. M.: In that it at times produces uncomfortable symptoms, yes, I suppose it is. But in that the hypotensive effects of the drugs are fully active only when assisted by gravity, postural hypotension is also an integral part of the treatment. The postural hypotension is, of course, due to the abolition of a normal reflex, namely sympathetic vasoconstriction, to overcome the gravitational effect of the upright posture. One also sees additional falls of blood pressure after meals, presumably due to uncompensated splanchnic dilation. Since the lowest pressures are recorded only when blood pressure reduction is assisted to the fullest extent by gravity, the maximum safe dose must always be judged by the pressure *measured in the standing posture.*

Dr. C.: I take it, then, that the thing to do is to have the patient along at the time you would expect the effect to be maximal—I gather from Fig. 1 at about three hours.

P. M.: Well, that is better than entirely random readings but still not good enough. Casual blood pressure readings at outpatient or surgery are most deceptive. They are usually too high because of the emotional stimulus. In our clinic blood pressures are taken at one-half-hour intervals throughout the day in the lying, sitting, and standing postures. The patients attend every day for a period of two or three weeks till dosage is stabilized and then when necessary to check on the maintenance of blood pressure control.

Dr. X.: But surely you do not mean to suggest that we in private practice can take our patients' blood pressures half-hourly during the day?

P. M.: I was about to emphasize that although this is without doubt the most satisfactory method of assuring control in a hypertensive clinic dealing with considerable numbers of patients, management of individuals by private practitioners can be achieved by questioning the patient about the symptomatic response to the various trial doses. We use this method of control by symptoms in our routine outpatient work after the initial period of investigation is over.

It is found that a surprisingly close approximation to the ideal trough blood pressure (standing) can be obtained, without the use of a sphygmomanometer, by increasing the dose one small dosage increment at a time until the patient feels slightly faint in the standing posture. The correct dose is, in practice, one or at the most two dose increments less (see Table I) than the dose which induces a feeling of faintness when the patient is standing quietly at the time of maximum drug action. Such doses are entirely safe, for if the patient adopts the sitting or lying posture the blood pressure rises at once. It is in fact much more satisfactory to adjust dosage in terms of hypotensive symptoms in this manner than in terms of occasional casual readings.

TABLE I. INITIAL DOSES AND DOSAGE INCREMENTS OF METHONIUM COMPOUNDS

	INITIAL DOSE (MG.)		DOSE MAY BE RAISED BY INCREMENTS (MG.)		HIGHEST FINAL DAILY DOSE USED (MG.)		AVERAGE DURATION SIGNIFICANT ACTION (HR.)
	AS SALT	AS METHONIUM ION	AS SALT	AS METHONIUM ION	AS SALT	AS METHONIUM ION	
Pentapyrrolidinium bitartrate, oral	20	8.9	20	8.9	1,400	623	8 to 12+
Pentapyrrolidinium bitartrate, "retard" subcutaneous	3	1.34	0.5–1.5	0.22–0.67	140	62.3	8 to 12+
Hexamethonium bromide, "retard" subcutaneous	20	11.2	5–10	2.8–5.6	1,200	672	3 to 5
Hexamethonium bromide, simple aqueous subcutaneous	15	8.4	5	2.8	1,200	672	2 to 3
Hexamethonium chloride, simple aqueous subcutaneous	12	8.8	4	2.9	——	——	2 to 3
Hexamethonium bitartrate, oral	187	76.1	187	76.1	9,000	3,663	2 to 4
Hexamethonium chloride, oral	125	92.5	125	92.5	——	——	2 to 4

However, doctors in private practice can, and in this town do, arrange days when several hypertensive patients attend occasionally for tests, blood pressures being measured by doctor or nurse. One trained person can manage eight patients simultaneously. No one would suggest that it is impossible to treat hypertension without these elaborate arrangements, but day tests do make treatment a much more certain and satisfactory process.

Dr. A.: How should I actually start my patient in terms of dosage if it should be necessary to give pentapyrrolidinium?

P. M.: Table I shows the dosage of the various methonium compounds which might help at this stage. I would give one-half of a 40 mg. tablet in the morning on the first day and note the effects during the morning. If, after lunch, the pressure had not fallen sufficiently as judged by symptoms or by blood pressure measurement if a test is performed I should give another half tablet. Then I should give a whole tablet in the evening and again the next morning, increasing by one-half tablet a time as necessary. The major doses are given in the morning and evening and a smaller supplementary dose after lunch. Her final regimen might be 180 mg. morning and 220 mg. evening with a supplementary 80 mg. after lunch. The morning and evening doses should be taken crushed up, in water, one-half hour before the meal to ensure as far as possible constancy of absorption. The smaller 40 mg. tablets can be divided into two and usually give a sufficiently accurate degree of adjustment. However, accuracy with the methonium compounds is, as cannot be too much emphasized, critically important, and at times it is necessary to divide them into four. This can be done by dissolving them in a measured amount of water. The larger 200 mg. tablets should not be divided.

OL.
1
955

Dr. C.: You say you can manage most of your patients who need it on oral pentapyrrolidinium?

P. M.: Yes, about 80 per cent can be managed orally.

Dr. F.: Does this include "malignants"? How did you start that patient of mine?

P. M.: We admit "malignants" and patients with congestive failure to hospital for initiation of treatment and start them off at once on a methonium compound parenterally. The initial dose and increments of the various injectable preparations are shown in Table I, which also illustrates the relationship between oral and parenteral doses. Again we now use almost exclusively pentapyrrolidinium. Its action is delayed by suspension in polyvinyl pyrrolidone and still further by the addition of 0.5 per cent ephedrine. The action of the "retard" preparation of pentapyrrolidinium is usually at its maximum at about two and one-half hours after subcutaneous injection, and a fully effective dose which lowers the pressure to 120 systolic may exhibit some hypotensive activity for twelve hours or more. There are a few patients who can never manage on the tablets, either because alimentary side effects make absorption inconstant or because they do not absorb enough that way. We do not like individual oral doses to go above 600 mg. The high degree of accuracy in dosage necessary with parenteral therapy requires the use of a tuberculin syringe graduated to 0.01 ml. Patients learn to measure their dose very satisfactorily. Fully effective therapy depends on maintenance of the gravitational effect during the night, and this can be managed even at home by propping the patient up into the sitting posture with a back rest inclined at forty-five degrees. A bolster is placed under the mattress so that the buttocks are supported and the patient does not slip down in bed. If the patient cannot manage the sitting posture, the head end of the bed is raised on blocks one foot, four inches high.

We think this deliberate use of posture to increase the extent of blood pressure reduction with safe doses is an essential part of treatment. It seems to have prevented the development of the so called "methonium lung" in our series of nearly 400 treated patients.

Dr. B.: Do not patients become tolerant of the methonium compounds after a while?

P. M.: Tolerance develops rapidly and must be countered by frequent increases of the dose using the increments shown in Table I. The dose will have to be raised daily at first, later less frequently. The development of full tolerance may take several months and the final dose may be many times that initially effective. Cross toleration is developed to some extent between hexamethonium and pentapyrrolidinium, but it is incomplete, and when full toleration has been achieved to either of these substances, it will be found on changing to the other substance that full toleration has not developed and further increase of dose will be required in order to preserve the full hypotensive effect.

Dr. X.: Even if postural hypotension is not conceded as an undesirable side effect you must agree that the parasympathetic side effects are very trying.

P. M.: On effective methonium therapy it is generally agreed that most patients have some side effects. In the majority of patients who are on a well-controlled regimen, however, the benefit they themselves experience from reduction in blood pressure outweighs the discomfort of side effects.

Dr. B.: Constipation is the great trouble my patients on hexamethonium have complained of. Is there any effective way of dealing with this?

P. M.: Pentapyrrolidinium is less likely to cause constipation than hexamethonium, in fact exceptionally it causes diarrhea. Constipation is more severe with oral dosage, and when individual oral doses necessary for adequate control of blood pressure go above 600 mg., we have found it desirable to change to parenteral therapy for at least one dose in the day because of the risk of paralytic ileus. However, when constipation is troublesome it is usually met adequately by the daily administration of the lowest effective dose of whatever laxative the patient finds suitable. When necessary, parasympathetic-stimulating drugs may be useful for combating constipation and also for dryness of the mouth. We have used oral prostigmine 15 mg., carbachol 0.25 mg., or 1 mg. pilocarpine in water up to three times a day before meals. Some degree of blurring of vision is usual. Physostigmine drops, 1/32 per cent or 1/16 per cent, may help, but it may be necessary to provide an extra pair of glasses, refraction being adjusted to the change in the eye brought about by the methonium compounds.

Reserpine has proved very useful in combating side effects. After addition to the regimen in people already on pentapyrrolidinium, the response to the pentapyrrolidinium is enhanced, so that smaller doses are effective. Side effects are consequently diminished. In three-quarters of the patients previously on pentapyrrolidinium alone, the combination was better either in respect to control over the blood pressure level or freedom from side effects.

VOL. 1 1955

Dr. C.: Does retention of urine ever occur?

P. M.: Rarely to an important degree except when there is already some interference with micturition, as from prostatic enlargement or a neurological lesion. In such cases it is desirable to relieve obstruction, if necessary surgically. Diminution in libido and potentia also occur very frequently, and in older men loss of sexual desire and capacity is usually complete. Younger men are handicapped to some degree but it is not often a source of distress.

There are one or two practical points worth mentioning about methonium therapy. The postural hypotension is increased in degree by salt-free diets or by infective processes during which there may be a considerable increase in methonium effect necessitating temporary decrease in dosage.

Dr. E.: You have so far made no mention of the place of surgery in the treatment of hypertension.

P. M.: We feel that the effective drugs now available effectively used replace surgery.

Dr. C.: What about veratrum and hydralazine?

P. M.: The veratrum alkaloids are very powerful hypotensive agents, but unfortunately hypotensive doses usually induce toxic effects, mainly vomiting, and with continued administration the gap between hypotensive and toxic doses seems to narrow.

As for hydralazine, in our experience, when it is used alone, the acute side effects (particularly headache) are prohibitive. Although it may well be effi-

TABLE II

1. *Uncomplicated Phase*		
a. Asymptomatic	High B.P., especially high basal B.P., especially males	Treat: Reserpine if adequate, or pentapyrrolidinium—reserpine
	Not so high B.P., especially low basal B.P., especially females	Reassurance, possibly reserpine
b. Symptomatic	Due to hypertension and meriting complicated regimen of treatment	Reserpine-pentapyrrolidinium, possibly reserpine alone
	Not due to hypertension, not meriting complicated regimen	Symptomatic treatment, reassurance, possibly reserpine
2. *Complications*		
a. Cardiovascular	Congestive heart failure	A strong indication for pentapyrrolidinium
	Cardiac asthma	A strong indication for pentapyrrolidinium
	Angina	An indication for pentapyrrolidinium; helpful in 50% or more
	Arteriolar changes	Favors therapy; reserpine or pentapyrrolidinium
	Exudative retinal changes	A strong indication for pentapyrrolidinium or reserpine-pentapyrrolidinium
b. Arteriolosclerotic	Renal changes	Not a contraindication to treatment but an indication for caution
3. *Accelerated Phase*		
a. Encephalopathy		An indication for pentapyrrolidinium or reserpine-pentapyrrolidinium
b. Without nitrogen retention		An indication for pentapyrrolidinium or reserpine-pentapyrrolidinium
c. With nitrogen retention		Not a contraindication to treatment but an indication for caution

cacious in combination with hexamethonium as a form of long-term therapy, the late toxic manifestations which have been widely encountered make us unwilling to use it.

Thiocyanates and the adrenolytic agents such as dibenzylene are not sufficiently active to compete with the others.

Dr. X.: Dr. Perera in his introduction gave us a very useful and practical classification of hypertension. Could you orientate your ideas about treatment in relation to this classification?

P. M.: This is a little difficult because some of our indications for treatment cut across the boundaries of Dr. Perera's scheme. However, in Table II we try to answer this question.

Senior P. M.: Let me close by summing up briefly. We believe that the methonium compounds are the most effective agents at present available for the treatment of severe hypertension and, of these, pentapyrrolidinium is the best. Reserpine alone is adequate for the management of a minority of cases, mostly mild ones, but in combination with pentapyrrolidinium provides probably the best regimen for control of blood pressure so far available. The main disadvantage of reserpine is the complication of depression, sometimes making necessary mental hospital care. Pentapyrrolidinium, as is true with the other methonium compounds, depends on gravitational effect for its full action. It is only by reducing blood pressure at the time of maximum activity to fully normal levels in the erect posture that an adequate duration can be assured of the blood pressure lowering effect. Dosage regulation in terms of subjective feelings of faintness in the standing posture is a much better indication of an adequate dose than occasional blood pressure recordings at the doctor's office. Where there are no facilities for frequent tests by technicians, it is nevertheless advisable to have occasional tests of half or whole day's duration at the doctor's office.

With some drugs you can get results and keep out of trouble on the wrapping paper instructions. This is not the case with pentapyrrolidinium. Approximations which are fully satisfactory for most drugs are most unsatisfactory for methonium salts. I would like to assure you all that the patients of a well-run hypertensive clinic are not miserable handicapped creatures suffering under a treatment worse than the disease. Methods of control which are good enough for most drugs are not good enough for ganglion blockers. With a dosage scheme designed for the individual patient and with attention paid to certain other features of management, it is possible in most patients to get a good control over blood pressure levels with comparatively few side effects. Perhaps one-half the patients are easy and the rest have to be worked on—but the time spent certainly brings results—and gratitude in a majority of patients.

VOL
1
195

REFERENCES

1. Smirk, F. H.: Practical Details of the Treatment of Hypertension by Hexamethonium Salts and by Pentamethylene 1:5-bis-N-(N-Methyl-pyrrolidinium) Bitartrate (M. & B. 2050A), New Zealand M. J. **52**:325, 1953.
2. Smirk, F. H.: Blood Pressure Reduction in Arterial Hypertension by Hexamethonium and Pentapyrrolidinium Salts, Am. J. Med. **17**:839, 1954.
3. Doyle, A. E., Smirk, F. H., and McQueen, E. G.: Treatment of Hypertension With Reserpine, With Reserpine in Combination With Pentapyrrolidinium, and With Reserpine in Combination With Veratrum Alkaloids, Circulation **11**:170, 1955.

METHONIUM TREATMENT OF SEVERE AND MALIGNANT HYPERTENSION

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OL.
1
955

When methonium treatment was first introduced we began to use the oral dosage suggested by Campbell and Robertson.[1] The results were unsatisfactory and patients frequently ran into trouble, which was far from easy to manage, and there were, in fact, some tragedies. The most troublesome complication was bowel paralysis; once this had set in with oral dosage, continued absorption of the drug could go on for days, as was demonstrated by Morrow, Schroeder, and Perry.[2] This led to prolonged and severe ileus, which could be fatal.[3,4] The sudden onset of faintness in a lavatory, where an unconscious patient could be reached only after an hour or so, led to virtual decerebration.[5] Experiences such as these led us to regard the alimentary absorption of the drug as too irregular, swinging unpredictably between ineffective control of blood pressure and dangerous overdosage. We learned, however, that there was something to be gained if dosage of the drug could be better controlled. We feel that we owe much to the early work of Smirk[6] on the methods of parenteral administration, for otherwise a most valuable remedy might have been given up.

Parenteral therapy was begun in this clinic in January, 1951. Because of the somewhat burdensome nature of the regimen we decided to limit its use to young and middle-aged benign hypertensives whose illness was complicated by *left heart failure, retinitis, or transient encephalopathic attacks, or malignant* and premalignant hypertension.[7] In such patients it was felt that prognosis had become sufficiently poor to justify the recommendation of a regimen making considerable demands on intelligent cooperation by the patient and bringing in its train other manifestations creating difficult management problems for the doctor in charge. We have never started methonium treatment in symptomless or uncomplicated hypertension, and time seems to confirm the wisdom of this restrictive selection. Patients with major cerebrovascular accidents and residual hemiplegia are not subjected to drastic blood pressure reduction, for we have seen such symptoms as dysphasia and paralysis intensify during low-pressure phases. Similarly, we hesitate to recommend drastic treatment in patients with cardiac ischemia and angina. Precordial pain and even myocardial infarction have developed while blood pressure is low. If such patients are given

methonium, great care should be taken to avoid excessive blood pressure reduction, and it is possible that some improvement of symptoms may be achieved by such means.[8] Experience has shown that such complications of arterial wall damage as thrombosis, hemorrhage, and dissecting aneurysm still occur in hypertensives under drug control; for this reason patients over 60 years are seldom accepted for vigorous blood pressure reduction. In the survey by Burgess[9] it was noted that hypertension of eight years' or more duration at the age of 65 did not reduce average life expectation. Gallavardin[10] is responsible for the idea that the onset of arteriosclerosis in some way protects against a malignant evolution of hypertension.

Methonium-induced hypotension controls the following hypertensive manifestations in descending order of efficacy:

1. Retinitis.
2. Heart failure.
3. Headaches.

There is, as yet, no proof that the following manifestations are ameliorated by the drug:

4. Encephalopathic attacks: responses are variable, possibly dependent on variable underlying pathogenesis.
5. Anatomic changes in vessel walls leading to thrombosis, cerebral hemorrhage, or dissecting aneurysm.

The following remain unaltered:

6. Residual cerebral softening.
7. Mental deterioration associated with cerebrovascular disease.
8. Renal damage.
9. Progressive and extensive renal arteriolonecrosis with rapidly developing uremia.

In amplification of the last statement it should be realized that progressive renal impairment is not an essential component of the clinical syndrome of malignant hypertension. The earlier pathologic descriptive term—"malignant nephrosclerosis"—included the severe vascular renal damage seen at postmortem, but there is no need to assume the presence of this advanced or terminal pathologic state in making a clinical diagnosis. Such an assumption would have no more justification than the suggestion that progressive pancarditis occurs in every case of rheumatic fever. Malignant hypertension is diagnosed by the presence of hypertensive neuroretinopathy (Grade IV changes of Keith Wagener and Barker, 1939). Their review of the evil prognosis and short expectation of life associated with these retinal changes fully justifies the diagnostic label. Treatment of malignant hypertension will only be successful in the absence of *progressive* uremia. That moderate uremia does not rule out successful management is indicated by the following history:

CASE 1.—F. H. T., a male house painter, aged 39, was first seen March 19, 1951. There was a history of nephritis in 1940. In January, 1951, he developed headaches, and later blurring of vision. There was no dyspnea.

VOL 1 195

On examination: Grade IV retinopathy. Blood pressure 230/140. No signs of heart failure; slight cardiac enlargement. *Urine:* Albumin +++, no abnormal deposit. Blood urea 82, 84, 86 mg. per 100 ml. *Roentenogram of chest:* moderate left ventricular enlargement. *Electrocardiogram:* L.V. ++. Hypodermic hexamethonium was started on March 25, 1951, and gradually increased to 200 mg. thrice daily. He has been on this dose ever since except for one month in 1952 when he developed "methonium lung" (Case 1: Doniach and associates,[11] 1954). Within two months his papilledema had gone, and a recent examination (December, 1954) revealed only Grade II changes. His headache has been much relieved, and apart from slight dyspnea, which does not interfere with his working capacity, he has no symptoms. Twice yearly blood ureas since 1951 were: 82, 92, 108, 106, 101, and (October, 1954) 103 mg. per 100 ml. The heart has not enlarged further and the electrocardiogram is unchanged.

If gross uremia with blood urea over, say, 130 mg. per 100 ml. is present from the time of recognition of a malignant phase, it is improbable that treatment will be successful in prolonging life. Even in those who have Grade IV fundus changes and cardiac manifestations, but with no gross uremia (blood urea under 110 mg. per 100 ml.), a rising blood urea may become manifest after the institution of hypotensive treatment and such patients continue a downhill course in spite of methonium control of blood pressure. This is illustrated by the following record:

CASE 2.—W. K., a male paint maker, aged 55, was first seen on July 5, 1954. In 1950 he had had giddiness and later lethargy and severe headache. Five weeks before admission, his sight became blurred and he was dyspneic on exertion. *On examination:* Mentally euphoric and aggressively talkative. Marked thickening of peripheral arteries. Grade IV retinopathy. Heart little enlarged and no signs of failure. *Urine:* Albumin ++, erythrocytes and some casts. Maximum S.G. 1.018. Blood urea 51 mg. per 100 ml. *Roentgenogram of heart:* Some left ventricular enlargement. Electrocardiogram showed left ventricular strain. Pentolinium was commenced on July 24, 1954, but caused some dysphasia. Subsequently he became unruly and severely disorientated, although there were no consistent focal neurological signs. This state ultimately settled down three to four days after the drug was stopped. The drug was restarted on Aug. 3, 1954, without any recurrence of the upset, but with some transient diarrhea. Although the blood pressure was well reduced and the papilledema cleared up (Aug. 29, 1954) the uremia progressed relentlessly and rapidly—stopping the drug did not arrest this—and the patient died on Sept. 16, 1954. Autopsy confirmed the diagnosis of malignant essential hypertension.

The patient most likely to benefit from methonium treatment, therefore, is a subject between the ages of 30 and 55 with hypertensive retinitis and predominant cardiac strain, without severe arteriosclerotic complications such as angina or cerebrovascular accidents, and without renal impairment. Patients are in the hospital for the first two or three weeks, during the early days of which "control" readings of pressure are made and any necessary investigations completed to exclude such removable primary causes of hypertension as unilateral renal disease and pheochromocytoma.

Pentolinium (pentapyrrolidinium, Ansolysen, M&B 2050A), which is largely replacing the earlier methonium regimen,[12] is now the drug of choice. It has the same general pharmacologic actions as hexamethonium, but has the advantage of being effective in about one-tenth the amount, weight for weight. This is of inestimable advantage in reducing the bulk of the self-injected dose. Injections are begun usually with 2.5 to 5 mg. pentolinium at eight-hour intervals.

Dosage is stepped up quickly to the level necessary to bring down the *standing* blood pressure to 140/90 or thereabouts. At first patients may complain of giddiness on standing, but soon they learn to tolerate nearly normal blood pressure levels. Throughout the day patients must be ambulant or at least sitting in order to take advantage of the postural drop in blood pressure. Increasing doses are usually required over the first three weeks, after which sensitivity is maintained indefinitely at a steady level. Minor adjustments may have to be made to meet the peripheral vasodilator influences of hot weather, to which these patients become sensitive, and psychologic disturbances may increase the amounts required. The range of dosage is wide. Some patients continue to respond to 10 mg. pentolinium or even less, while at the other extreme we have two patients (both young women) requiring 175 mg. pentolinium as an effective dose.

Side effects are met by appropriate pharmacologic means: dry mouth by urethane of β methyl choline tablets (25 mg.) swallowed at the time of the injection; accommodation paralysis by special spectacles; constipation by suitable purgatives, e.g., aloin pills; and colic by atropine tablets. In all this the patient has to be instructed and guided. He gets the following printed instructions:

INSTRUCTIONS TO PATIENTS ON METHONIUM OR ANSOLYSEN TREATMENT

"1. This drug is given for high blood pressure. High blood pressure by itself is a condition which need not cause anxiety and people can have it for many years without coming to any harm. Treatment is only necessary when it shows signs of doing damage and if you can co-operate in helping the doctors a good deal can be achieved towards making the condition harmless once more. Hexamethonium and Ansolysen (two similar substances) are used for this purpose.

"2. In order to obtain the best effect, the injections should be given quite regularly at the times recommended by the hospital, and you should not alter your dose without consultation.

"A certain number of unpleasant effects from the drug are unavoidable from time to time, but this should not interfere with the treatment. If these unpleasant effects become excessive, you should immediately get in touch with either your own doctor or the hospital and seek advice.

"3. For a short while after an effective dose, you will probably be unable to read without special glasses and your mouth will be dry. Troublesome dryness may be relieved by the tablets ('mecothane') prescribed at the hospital.

"4. As faintness and giddiness may occur on standing still, it is unwise to stand in queues, e.g. in shops, bus stops, etc., within 2-3 hours after a dose. However, it is quite all right—and in fact beneficial—to keep walking about during this time. It should not be necessary to lie down after an injection, and sitting quietly in a chair for a few minutes should be enough to relieve any feelings of faintness. Some degree of faintness is a valuable indication that the drug is working well, and that you are having a full dose.

"*The more you are on your feet the better, but keep moving about.*

"5. If you are recommended to take a very large injection on going to bed, make sure that you do not have to get up in the night. Keep a bed-pan or urine bottle at hand in case you need it. If the large night-dose is adequate you should still feel a little faint on your feet first thing in the morning.

"6. You may notice that hot weather, a hot bath or even eating a meal increases the feeling of faintness after a dose. These effects are quite expected, but avoid hot baths within four hours after a dose.

"7. Constipation is commonly produced or made worse by this treatment, and you should keep your bowels open by a regular dose of an aperient which suits you, e.g. liquid paraffin, vegetable laxative or salts. If this is not sufficient and there is constipation for three days or longer, it is permissible to omit one or two injections, when the bowels will probably act by themselves.

"8. Occasionally some difficulty in passing water may be experienced; always empty your bladder before an injection and do not let it get too full. (The tablets used for dryness of the mouth may also help the bladder to empty).

"9. If you develop a *feverish illness, halve the dose of the drug*, go to bed till your temperature is normal, then gradually raise the dose to the usual amount when you are better. During this adjustment, keep in touch with your doctor.

"10. If you have *diarrhoea or vomiting or both, take no injections till this has stopped*, and then recommence with *only one-quarter the usual dose*, and raise it gradually to the usual amount over the next day or two. Your hospital doctor will be glad to advise you on this.

"11. If for any reason the drug is discontinued for a number of days or weeks, make contact with the hospital before recommencing the injections, as the dose should be considerably smaller than usual to begin with.

"12. If you break your syringe, take the broken pieces to your National Health Practitioner, who will give you a prescription to obtain another one from a chemist.

"13. If you cannot keep your out-patient appointment, please write or telephone the hospital and make another one for as soon after the original date as possible.

"14. *In case of sudden illness or emergency* get a telephone message to this hospital to the ward sister on the ward in which you were an in-patient."

Attendance at a special follow-up clinic is arranged after leaving the hospital at suitable intervals, weekly at first, gradually lengthening the intervals according to progress, and contact is maintained to meet difficulties as they arise. At present in our clinic some seventy patients are under investigation and treatment. This requires, in addition to routine hospital facilities, the whole-time services of a medical registrar and nurse-technician working under a responsible consultant. At such outpatient attendances blood pressure responses are measured one-half to one and one-half hours after injection and the result in the standing position determines further dosage instructions. We disagree completely with Smirk[8] that blood pressure readings taken at these sessions are "worse than useless." On the contrary, a fall in pressure observed under these conditions is better evidence of pressure control than readings made under "basal" sedated conditions, a point which is also made by Freeman.[13]

In all patients with malignant hypertension injections are given three times a day for at least the first six months. In patients with mild renal impairment delayed excretion may permit satisfactory blood pressure control with only two injections in twenty-four hours. Once the acute phase is over and symptoms are receding satisfactorily some relaxation of the regimen seems permissible. A most useful regimen used over the last year or more is to give *double* the effective daily dose on going to bed at night with strict instructions against getting out of bed. This dose will reduce the recumbent blood pressure and on getting up in the morning a "hang-over" postural hypotension remains. The aim is to set this large night dose at a level which will be followed by a feeling of postural faintness on rising. When this is done an effective fall in blood pressure may be maintained for as long as sixteen hours. During the first half of the night the blood pressure is low even in recumbency, and the method has the additional advantage that the more troublesome side effects take place during sleep. A further injection in the early afternoon is all that is needed to get satisfactory total blood pressure control. In a few instances recently we have substituted an *oral* dose of pentolinium *in solution* in the afternoon. So long as the *major* part of daily treatment takes place by parenteral dosage, we feel that the risks of a single oral dose in solution at twenty-four-hour intervals are much less than the risks of control by oral dosage alone.

Intelligent patients learn the regimen remarkably well and by their own sensations can tell whether dosage is adequate or inadequate, and make minor appropriate dosage adjustments. It should be noted that the reduction of blood pressure achieved by these various regimens is of a *phasic* character. While more continuous reduction of pressure is theoretically possible by more injections, infusions, and the use of "retard" preparations, we have found that such regimens become intolerable. The patient requires some time each day when his autonomic system can work so that he can swallow his meals, read in comfort, and empty his bowels and bladder. Admittedly his pressure may be higher than desirable at such times, but the restoration of considerable fluctuations in pressure, with a few hours of "normality" of pressure in each twenty-four-hour period, may be all that is necessary to relieve the heart and restore severe hypertension to a more benign course.

RESULTS

Malignant hypertension remains a highly lethal disease. A significant number of patients have *progressive* renal damage by the time of recognition, and in such patients mere blood pressure reduction seems to be of no avail. Major cerebrovascular accidents may also put the patient beyond help. In those patients with predominant retinal and cardiac involvement and in whom renal damage is moderate (blood urea less than 100 mg. per 100 ml. and nonprogressive as determined by observation under treatment), results of treatment are most encouraging (see Case 1). Retinitis subsides, heart failure regresses, and kidney function remains unchanged. Death, however, may still occur from cerebrovascular accidents or dissecting aneurysm. Coronary thrombosis

is unusual in malignant hypertension. Another cause of death is organizing edema of the lung.[11] Fig. 1 shows that, of thirty-two patients beginning treatment, there is a fairly high early mortality, most commonly from uremia, which has become progressive, but after the first six months the chances of further survival seem to be considerably improved over those of a matched control series. The control series consists of thirty cases from our own clinic records in the years immediately prior to 1951, and comparable in all respect to the treated series, but who were not subjected to any form of hypotensive therapy. Four patients in all have survived beyond three years and one is now reaching four years' survival. Three of these are well and at full work.

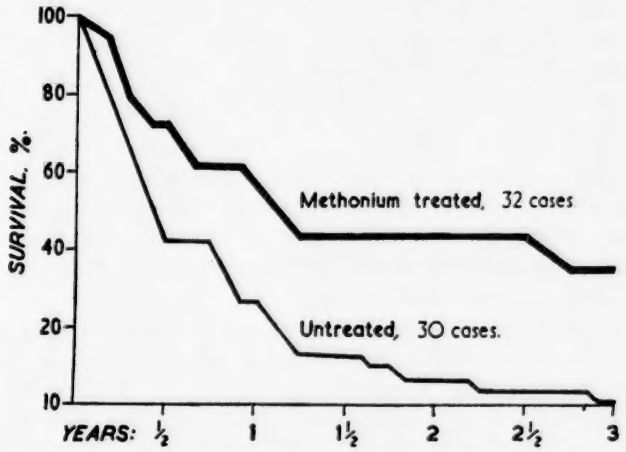

Fig. 1.—Expected survival of malignant hypertension without gross initial uremia (B. U. < 110). Plotted from our data tabulated as a survivorship table.[17] Read "O" instead of "10" on survival scale.

Difficulties, of course, arise and sometimes treatment has to be abandoned. Poor initial intelligence, or mental disturbances as a result of cerebrovascular disease, gross cerebrovascular accidents, uncontrollable bowel symptoms or bladder trouble, and the development of progressive uremia, other accompanying disease like severe chronic bronchitis, have all been responsible for decisions by patient or doctor to stop the drug. Two of the patients in the treated series who had survived over one year died within a short time of abandoning treatment. In spite of these troubles the gain in length of life seems to be becoming clear. In addition to mere survival, the feeling of relative well-being which accompanies recovery of vision, disappearance of headaches and cardiac symptoms makes the course of the illness vastly different from the downhill misery experienced by the longer survivors of the "untreated" controls. The following record illustrates the best type of result:

Case 3.—D. S., a female hairdresser, aged 32, was first seen Dec. 2, 1952. There was a history of toxemia in her two pregnancies (1942 and 1945) with residual hypertension. She had had severe occipital headaches for one year, blurred vision for three months, exertional dyspnea

for one month, and nocturnal dyspnea for a fortnight before admission. On examination, she was in congestive failure with dependent edema. Blood pressure was 230/160. The heart was grossly enlarged with a gallop rhythm. Grade IV retinopathy. *Urine:* albumin ++, a few erythrocytes, no casts. Blood urea 21 mg. per 100 ml. Roentgenogram of heart and electrocardiogram showed considerable left ventricular enlargement. Methonium tolerance led to use of an analogue ("M & B 1950") which was more effective, Digoxin and mersalyl being also given. Symptoms and papilledema regressed. In April, 1953, pentolinium, 60 mg. thrice daily, was started. She did so well that in April, 1954, the regimen was modified to 170 mg. at night hypodermically, and one oral dose of 600 mg. in solution at midday. When last seen (Dec. 17, 1954) her fundi were normal, she had no headache, and although her triple rhythm persisted, she had little dyspnea and was capable of doing quite an exacting day's work. Both roentgenogram of heart and electrocardiogram were much improved.

NOTES ON OTHER FORMS OF HYPOTENSIVE THERAPY

"Retard" Methonium Preparations.—Delayed absorption of methonium in colloid solutions in polyvinyl pyrrolidone was disliked by our patients, who complained of irregular timing of effects and also that self-injection was more difficult due to the "sticky" solution.

Veratrum Compounds.—As methonium is contraindicated in pregnancy because of its effects on the fetus, severe hypertension in pregnancy is usually treated by one of the newer veratrum derivatives. It is, however, a difficult drug to use as the margin between an inadequate dose and one producing severe gastric upset with hypotension is narrow.

Reserpine alone has not been a convincing hypotensive agent in tolerable doses. Nonetheless, its vasodilator influence may become manifest when homeostatic pressor reflexes are depressed by methonium. Other writers[14] claim therapeutic benefit from the combination of methonium and reserpine. So far we have had too little experience to make any pronouncement.

Hydralazine was found to be of little value in itself by Khan.[15] Some patients having difficulty with methonium were put on hydralazine, but found the side effects less tolerable and asked to be put back on methonium. Convincing and sustained fall in blood pressure was never achieved.

Salt Restriction.—We have found salt restriction of value as a temporary measure only. It cannot be tolerated indefinitely. Smirk[16] stated that it enhances the effects of methonium; we have preferred to achieve our effects by higher dosage rather than by the imposition of a tasteless, unpalatable diet.

Sympathectomy.—We have not recommended sympathectomy for four years.

SUMMARY

1. The principles of methonium or pentolinium treatment of severe and malignant hypertension are reviewed, with emphasis on practical details.

2. Certain hypertensive manifestations such as headache, retinitis, or cardiac strain are reversible by phasic reduction of blood pressure. Other damage of an anatomic character in blood vessels and other tissue may be irreversible.

3. Results are reviewed in malignant hypertension without severe initial uremia. While there is still a high mortality in the early months of treatment,

VOL. 1 1955

the prospects of further survival after six months are considerably improved. Amelioration of retinitis and heart failure often permits return to full activity.

4. Other medical therapeutic measures have been reviewed but the results fall far short of those achieved by parenteral methonium.

REFERENCES

1. Campbell, A., and Robertson, E.: Brit. M. J. **2**:804, 1950.
2. Morrow, J. D., Schroeder, H. A., and Perry, H. M.: Circulation **8**:829, 1953.
3. Mackey, W. A., and Shaw, G. B.: Brit. M. J. **1**:1205, 1951.
4. Thomas, O. M., and Williams, R. G.: Brit. M. J. **1**:1331, 1951.
5. Ball, J. D.: Lancet **2**:650, 1950.
6. Smirk, F. H.: New Zealand M. J. **49**:637, 1950.
7. McMichael, J.: Brit. M. J. **1**:933, 1952.
8. Smirk, F. H.: New Zealand M. J. **52**:325, 1953.
9. Burgess, A. M.: New England J. Med. **239**:75, 1948.
10. Gallavardin, L.: La tension artérielle en clinique, Paris, 1920, Masson & Cie.
11. Doniach, I., Morrison, B., and Steiner, R. E.: Brit. Heart J. **16**:101, 1954.
12. Morrison, B.: Brit. M. J. **1**:1291, 1953.
13. Freeman, Z.: Lancet **2**:145, 1952.
14. Doyle, A. E., and Smirk, F. H.: Lancet **1**:1096, 1954.
15. Khan, M. A.: Brit. M. J. **1**:27, 1953.
16. Smirk, F. H.: Lancet **2**:477, 1950.
17. Hill, A. B.: Principles of Medical Statistics, London, 1952, Lancet, Ltd., p. 174.

CURRENT TREATMENT OF ARTERIAL HYPERTENSION

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VOL
1
195

I GATHER that the editor's invitation to participate in this symposium carried with it the desire for informality, freeing me from the necessity of a systematic presentation of the current methods of treating hypertension.

Three impressions have recently become crystallized in my mind. The first is that a major "break-through" has been achieved in lowering elevated blood pressure and that in the course of the next few years we should know whether this alters the ultimate outlook for the hypertensive. Second, advertising claims for the antihypertension drugs have, in many instances, been so preposterous and biased that the physician has come to expect miracles with a minimum of effort on his part. He has been led to believe that the treatment of hypertension is sure and simple. Let him study Fig. 1 to see that it is not.

The virtues of one derivative compound over another are even backed by leading medical societies. Virtue in the merchandizing aspect of treatment, I fear, has not been rewarded. It is also high time the investigator's neurosis called "the-first-to-test" be recognized for what it is, a necessary function requiring about as much creative imagination as preparing instant coffee. Third is loss of the educational value of the physician-patient relationship. Bottles of medicine are offered as replacement; this does not suffice! Hypertension is still a chronic disease with arteriosclerosis an integral part of the process. Its casual management and the un-understanding acceptance of current therapy will inevitably leave in its wake many miserable patients in whom the changes wrought are largely those in the pocketbook.

MILD ARTERIAL HYPERTENSION

Two problems arise in deciding on the treatment of mild arterial hypertension. The first, and probably the more important, is whether the cardiovascular disease associated with the hypertension is advancing significantly or whether it is essentially static.

I have seen a number of patients who had mild hypertension (160/100 mm. Hg) twenty-five years ago whose blood pressure is now about the same, or lower. These people needed no treatment and might have fared less well had they been

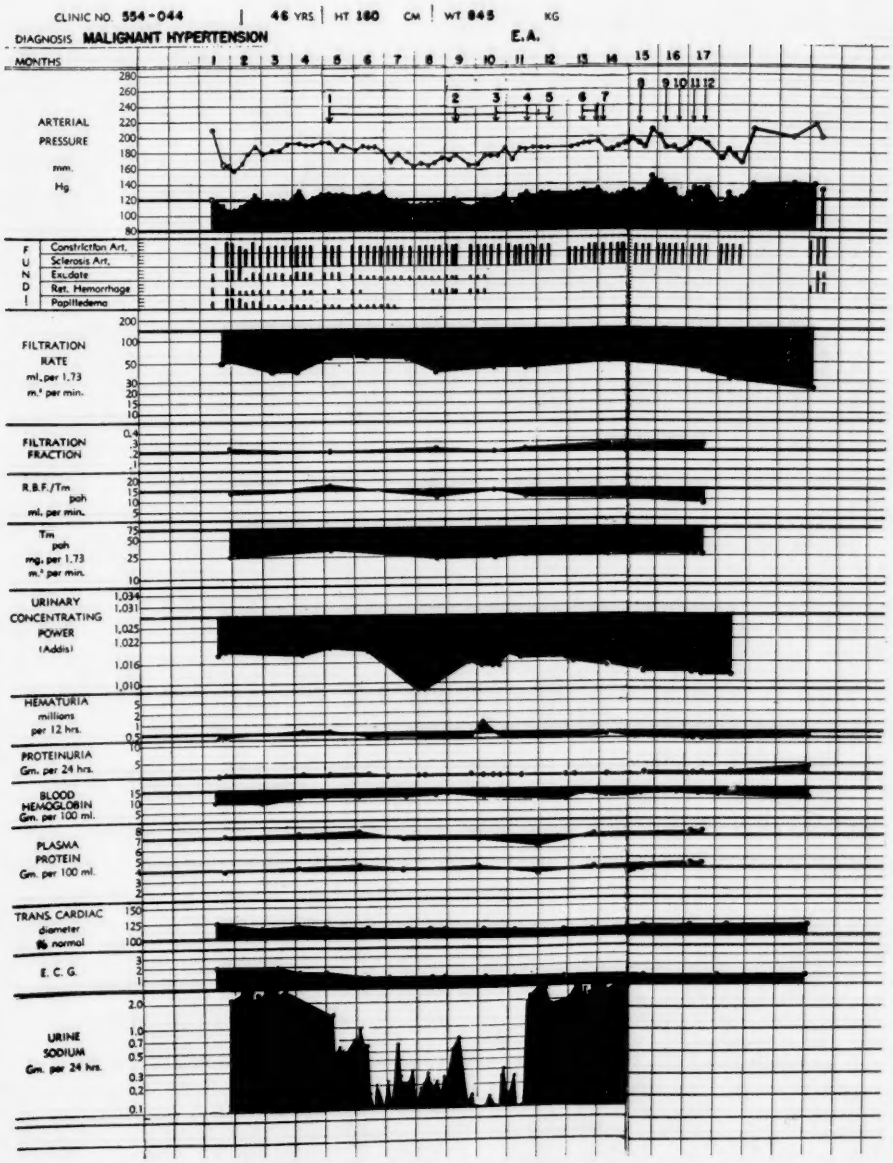

Fig. 1.—Example of the failure of two forms of treatment which seemed to be properly selected in a patient who faithfully cooperated. While the eye grounds cleared, sixteen months after treatment was initiated he died of cardiac failure. The average diastolic blood pressure was not reduced below 120 mm. Hg during his long stay in hospital. *1*, Rice diet; *2*, plus Lonalac 30 Gm.; *3*, plus Lonalac 60 Gm.; *4*, plus Lonalac 60 Gm. plus NaCl 8 Gm.; *5*, low-salt diet plus Lonalac 60 Gm. plus 8 Gm. salt; *6* and *7*, Low-salt diet plus Veriloid; *8*, low-salt diet discontinued; *9*, enteric Veriloid; *10*, enteric Veriloid discontinued; *11*, cortisone; *12*, cortisone discontinued.

The addition of neither milk protein nor sodium chloride affected his average blood pressure (*2-5*), nor did Veriloid injections have a significant effect. The patient died of the combined effects of cardiac and renal failure, although these were never extreme.

given some of the modern antihypertensive drugs. While hypertension is more common in women than men, in most cases it is certainly milder and less inclined to progress. Many of them live out a normal lifespan. In some of them there is little or no progressive vascular disease.

Contrasting with these patients are those with somewhat higher arterial pressure in whom the cardiovascular disease progresses relentlessly, especially in men, although at varying rates. Such patients require early treatment. There is a much smaller group of middle-aged women in whom hypertensive vascular disease may be rapidly fatal.

Treatment of the early phases of disease is always a sound principle and if a remedy were available that would surely lower blood pressure to normal without long-term injurious effects, hypertensive patients ought to be treated before vascular disease has developed. The alkaloid reserpine has currently been suggested as one fulfilling such requirements. While the toxic effects of reserpine have been few, still it has produced severe mental depression and Parkinsonism in some patients. These cannot be considered minor toxic actions. The increase in appetite and nasal stuffiness may be annoying but often are overshadowed by the feeling of mild drunkenness and fatigue exhibited by some patients. It is evident that it has been insufficiently studied to allow conclusions as to its long-term toxic effects. Its effectiveness as a hypotensive drug does not extend to all patients. Thus, if treated as an investigation, the trial of reserpine in early hypertension would be justified. But its indiscriminate recommendation and use, backed by nothing more than guess, are certainly unjustified.

Currently, therefore, the early phase of hypertension seems best managed by a combination of those general measures of social and spiritual readjustment that any wise physician will prescribe. Along with these, phenobarbital as a mild sedative, acetyl salicylic acid or potassium thiocyanate,[1] and/or "head-up bed" for headache complete the immediate treatment. It is of great importance that the patient be re-examined regularly to determine the rate of progress of the disease.

SEVERE HYPERTENSION WITH PROGRESSIVE CARDIOVASCULAR DISEASE

These patients require active and prolonged treatment. We have described elsewhere[9] our "severity index" which reflects in a single figure the over-all status of the cerebral, cardiac, and renal vascular beds. The aim is to avoid the common fallacy of basing conclusions wholly on arterial pressure or eye-ground changes, while avoiding the need for cumbersome exposition concerning concurrent vascular pathology in the body. A maximum of four points each is assigned to estimates of average supine diastolic pressure and of the extent of hypertensive vascular disease in the heart, kidneys, and brain (Table I). For example, a patient with diastolic pressure averaging more than 140 mm. Hg, Grade IV heart failure, uremia, and Grade IV retinopathy, plus encephalopathy, would be graded 16; improvement in any category reduces the grade below 16.

TABLE I. COMPOSITION OF SEVERITY INDEX

PANEL	POINTS			
	1	2	3	4
Diastolic average	96–110	111–125	126–140	140 or greater
Cardiac function	I	II	III	IV
Renal				
proteinuria	<0.5	0.51–1.0	11–3.0	>3.0
serum creatinine	<1.5	<1.5	1.6–3.0	>3.0
Cerebral				
fundi*	I	II	III	IV
signs	0	Headache	Old stroke	Fresh stroke
Total	4	8	12	16

*Keith-Wagener.

VOL.
1
955

The details of the manner in which the various drugs are used I shall omit since these will be found in other publications.[2,3,9] Rather I propose to describe briefly our reasons for the use of certain hypotensive drugs.

Since there is often some urgency in the treatment of hypertension with progressive vascular disease, we do not withhold the more potent hypotensive drugs until last. The patient is immediately placed on a drastic low-salt diet. If heart failure is not prominent, a course of hydralazine is started, ordinarily after a trial in the hospital on hydralazine placebo. If, after two or more months of hydralazine, no significant fall in arterial pressure has occurred, it is discontinued. A great deal has been made in the literature about the undesirable effect of hydralazine in increasing cardiac output. It is of interest to note that the most recent results of Crumpton and his group[4] show an increase in coronary blood flow and decrease in coronary vascular resistance without significant change in myocardial oxygen consumption or in cardiac work.

Most of our patients in the group treated with ganglion-blocking agents are also put on a salt-poor, and some on the drastic (200 mg.) low-sodium, diet. We employ the salt-poor diet to aid in preventing cardiac decompensation. We have no rational method of selecting the patients who will respond with a fall in blood pressure to these diets. From 20 to 25 per cent of those on the drastic low-sodium diet are improved by it alone in our experience.[5]

Hexamethonium or pentolinium may be started either after it has been shown that hydralazine is ineffective or, even if it is effective, after intravenous intramuscular test doses to determine sensitivity. If it is necessary to lower blood pressure rapidly, the drug is given subcutaneously or intravenously until the desired lowering is obtained and then it is continued by mouth. The patient sleeps in a "head-up bed" and is urged to walk and stand as much as possible to take advantage of postural hypotension. He must, of course, be warned of

the possibility of excessive postural hypotension. Elastic stockings or bandages help to keep this under control.

Patients vary widely in their initial hypotensive response to hexamethonium and pentolinium, and the rate at which tolerance develops also varies greatly. It is for these reasons that the dosage must be under constant scrutiny; perhaps giving too little to do an effective job is the more common error.

While many patients respond with a satisfactory fall in blood pressure with hydralazine, hexamethonium, or pentolinium, there are others who do not, or who do so for a period of only several months. We have always been surprised to find a higher percentage of such therapeutic failures in our own patients compared with those of other investigators.

Pentolinium has, in our hands, shown only modest advantages over hexamethonium,[16] although it is, weight for weight, some five times as active. Absorption seems to be somewhat more regular but its action is little, if at all, longer. Side effects as a result of parasympathetic blockade are quite as severe as with hexamethonium, and in this, our results agree with those of Birkhead and Allen.[6]

Reserpine[7,8,10] alone may cause a significant hypotensive action in something like 35 per cent of patients with moderately severe hypertension, from one to three weeks after initiating treatment. Severity of the hypertension does not appear to be the only determinant in the ability to respond. The addition of reserpine to hydralazine in patients who have responded favorably to the latter usually causes further fall in blood pressure, although this is much less likely in patients with malignant hypertension. Hexamethonium requirement may be decreased by addition of reserpine. The same is true of pentolinium. I say this with some reluctance because our data are not yet conclusive.

Reserpine alone seems effectively antipressor in some hypertensive patients but quite ineffective in many others.[11] The factors determining responsiveness to hydralazine or to pentolinium are not the same as those which effect response to reserpine. The same patient may respond to all these drugs, but those who respond to one do not always respond to the others. Currently, the literature abounds with conflicting reports on the antihypertensive efficacy of Rauwolfia and most commercial brochures continue to cull only those reports that are favorable. Rauwolfia is rapidly becoming the "wonder drug from India," a position it is not likely to retain. How much better it would be to place it in a secure berth where its merits and its demerits will be recognized.

We have not been able to demonstrate true synergism between any of the drugs currently in use either in patients or in animals. Their use in combination seems good in principle provided it is demonstrated in each patient that the drugs given singly are, in fact, effective. We oppose the use of mixtures, especially in tablet form, where the dosage cannot be separately varied. Hexamethonium does not give any significant protection against the disagreeable side effects of hydralazine.

Combining the action of reserpine with pentolinium gave Smirk[12] the best results yet observed with any of the antihypertensive drugs, whether given singly or in combination. It is especially to be noted that while the reserpine had little action itself, it reduced considerably the necessary dose of pentolinium

and thus reduced the side effects. If this is confirmed it will demonstrate synergism between the various hypotensive drugs in patients for the first time.

I have tried to demonstrate a synergistic effect of resperine on pentolinium in dogs anesthetized with pentobarbital without success. Four experiments (Table II) were conducted, as follows: The cardiovascular responsiveness to serotonin, noradrenaline, and very small doses of pentolinium was determined. Reserpine was given intravenously and the responses again ascertained. Even after repeated injections of reserpine, pentolinium showed no greater hypotensive responses than the control. Concurrently the responses to noradrenaline and serotonin were greatly augmented as a result of the small, repeated doses of pentolinium. These experiments seem to demonstrate conclusively that reserpine is not synergistic with, and does not augment the depressor action of, pentolinium in dogs under these conditions. I have found that reserpine has a similar lack of effect on response to hexamethonium.

OL.
1
955

TABLE II. THE CARDIOVASCULAR ACTIVITY OF SEROTONIN, NORADRENALINE, AND PENTOLINIUM IN A DOG GIVEN RESERPINE

DRUG	DOSE	TIME	INITIAL B.P.	CHANGE IN B.P.
Noradrenaline	10γ	2:23	138	+26
Serotonin	0.6 mg.	2:28	138	+22
Pentolinium	0.1 mg./kg.	2:37	140	−14
Noradrenaline	10γ	2:45	126	+30
Reserpine	0.1 mg./kg.	2:50	128	0
Pentolinium	0.1 mg./kg.	2:55	130	−14
Noradrenaline		3:07	120	+50
Reserpine	0.1 mg./kg.	3:09	120	0
Pentolinium	0.1 mg./kg.	3:23	108	−14
Noradrenaline	10γ	3:33	106	+64
Reserpine	0.1 mg./kg.	3:45	110	0
Pentolinium	0.1 mg./kg.	3:55	106	−12
Noradrenaline	10γ	4:14	94	+70
Reserpine	0.1 mg./kg.	4:20	98	0
Pentolinium	0.1 mg./kg.	4:29	92	−12
Serotonin	0.6 mg.	4:35	84	+46
Noradrenaline	10γ	4:40	86	+64

Smirk has always considered oral hexamethonium a poor form of treatment but now uses pentolinium with great enthusiasm. This has not been the general experience in this country. While pentolinium may have a few advantages, they do not appear so great as to separate the two drugs by such a wide margin. Indeed, in some investigators' hands, pentolinium shows no clear advantages.

From the literature it has been widely assumed that drug therapy is more effective during periods of salt restriction. This may be so, but it should be pointed out that so far this has not been conclusively demonstrated. Somewhat similar circumstances surround the use of sympathectomy, but again no convincing evidence has been offered in substantiation.

Occasionally we perform sympathectomy, the "total" of Grimson, or the partial of Adson and Smithwick, either because the patient has failed to respond to other measures or because he is unwilling to follow the rigid strictures of

drug therapy. We still think sympathectomy would have an important place in therapy if the current 25 per cent success rate could be converted to 95 per cent by proper selection of patients. The problem of "total" versus "partial" sympathectomy still remains to be resolved.

Our result with the veratrum alkaloids has not been satisfactory, in marked contrast with those of others.[13] Occasionally a patient has a partially sustained hypotensive response, but in our hands too few of such persons were found to justify an extended search for them. The dose required was so high to achieve improvement in the severity index, and nausea and vomiting were either almost constant or so close to it that the treatment did not seem practical. We do not deny that given every two hours, and with great care, or, as put by some investigators, "intelligently," reasonably satisfactory fall in blood pressure may occur for several months in some patients. But after that, tolerance developed in our patients without loss of the drug's ability to produce nausea. Even in these, if the dose is increased enough, sudden and severe falls in arterial pressure can occur. This adds to the difficulty of using the drug. I am unable to explain why our results have been so discouraging, while those of others are just the opposite. From the wide sale of these drugs we must be in a minority. We have seen the long-term, satisfying result too rarely to justify continuing the use of veratrum.

VOL. 1 1955

We have employed total adrenalectomy in a few patients. The most important observation we made was that in some patients with malignant hypertension, arterial pressure did not fall to normal despite the occurrence of adrenal insufficiency. This seems of sufficient interest from the point of view of theory of the mechanism of hypertension briefly to document such an experiment.

This patient had severe malignant hypertension but with good renal function. As shown in Fig. 2 in the section on arterial pressure (Nos. 1 and 2), he received a course of pyrogen therapy with fall in blood pressure and reduction of hematuria. A strict low-sodium diet was then instituted (No. 3) and then total adrenalectomy was performed at No. 4 (May 7, 1951). He was maintained on 50 mg. of cortisone, 20 mg. of ACTH, and 6 Gm. of salt a day. Three weeks after operation serum sodium was 130 meq. per liter and potassium 6.1 with signs of adrenal insufficiency. Still arterial pressure did not fall appreciably. On June 15, there was again adrenal insufficiency with no significant fall in arterial pressure.

Before adrenalectomy, intravenous injection of tetraethylammonium chloride elevated arterial pressure, instead of the more usual effect of lowering it; after operation both TEAC and hexamethonium chloride (25 mg. intramuscularly) lowered it very effectively. For this reason, at No. 5 the patient was treated with intramuscular injections of hexamethonium. The drug caused repeated gastrointestinal upsets, and the patient's general condition progressively deteriorated, more especially the renal function. He died on July 14. At autopsy the usual picture of malignant hypertension with necrotizing arteriolitis was found; secondary parathyroid hyperplasia, atrophy of the testes, and minimal coronary and aortic atherosclerosis were observed.

It seems to me this patient illustrates the important principles, by no means accepted by all, that even so drastic a change as adrenal insufficiency need not always be associated with a significant fall in arterial pressure and that the necrotizing vascular lesions are capable of progressing even when replacement corticoid therapy is minimal. In this particular patient the adrenal glands

did not appear to be primary in the mechanism of the disease. Did the great increase in response to ganglion-blocking agents indicate a change in mechanism after the loss of the adrenal glands? It is possible.

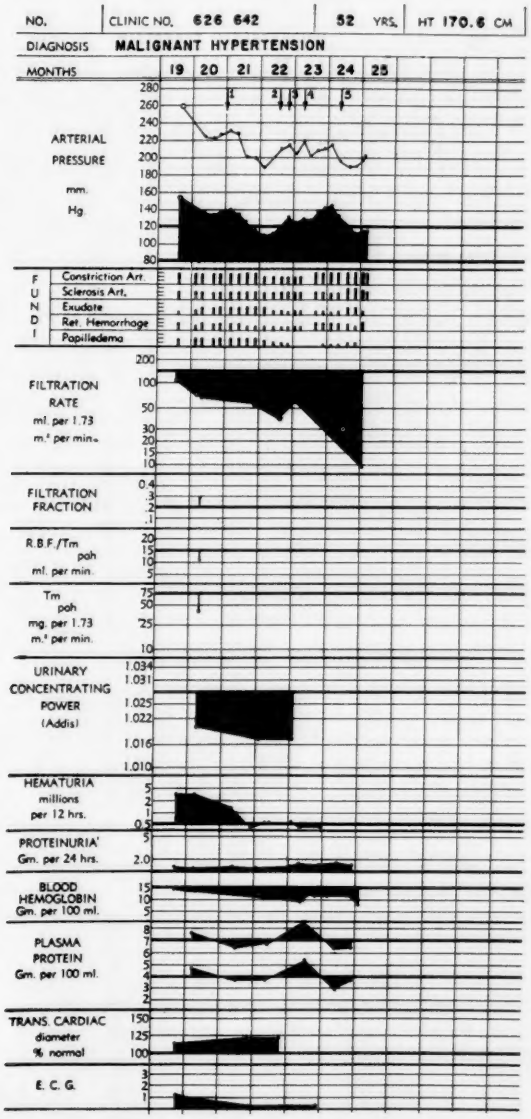

Fig. 2.—The effect of total adrenalectomy in a patient with malignant hypertension. At (*1*) pyrogen therapy was initiated and discontinued at (*2*). The low-sodium diet (Lonalac) was started at (*3*) and bilateral adrenalectomy performed at (*4*). At (*5*) treatment with parenteral hexamethonium was employed. Even though there were two levels of adrenal insufficiency, there was no drastic fall in average arterial pressure. The only impressive fall occurred during pyrogen administration.

I have documented this failure for a reason other than interest in the mechanism of hypertension. Publication of our failures as well as our successes would act to restore the balance of optimism and pessimism which is the essence of good judgment.

CEREBRAL EPISODES

Headache is first treated with aspirin and "head-up" bed; if migrainelike, Cafergot (ergotamine tartrate plus caffeine) is tried. An intravenous injection of 1 Gm. potassium thiocyanate is given if these measures fail.[1] I do not recall a single patient who has failed to respond.

We believe that lowering of arterial pressure is the most important part of the treatment of hypertensive encephalopathy. For that purpose, we have used sodium nitroprusside or hexamethonium. We prefer sodium nitroprusside because of the ease with which the height of the blood pressure can be regulated,[14] its cheapness, and easy availability. On the other hand, it must be given by constant intravenous infusion. If the patient is so restless that this is impractical, hexamethonium by vein or muscle is employed. We have not found other measures necessary.

We tend to treat cerebral hemorrhage conservatively with early initiation of rehabilitiation. Occasionally, after an arteriogram, a craniotomy has been performed for removal of a blood clot. The mortality in this group has been high, but we have no way of knowing whether it would not have been high whether or not an operation was performed. Good results have occurred in only two patients and the operation was performed early in these two. Stellate block was used regularly at one time, but we have largely abandoned it.

SEVERE RENAL INVOLVEMENT

It is well recognized that reduced renal function greatly lessens the chance of arresting the downhill progress of hypertensive vascular disease. Yet we are convinced that in some patients it is not a contraindication for the use of hypotensive drugs provided the renal insufficiency is not extreme. On the contrary, a few of our most dramatic results have occurred in patients with moderate elevation of blood urea.

There are a group of patients, composed in part of young women, in whom the renal disease advances rapidly and inexorably in spite of lowered blood pressure.

MALIGNANT HYPERTENSION

Malignant hypertension has lost some of its lethal qualities as the result of current antihypertensive therapy, although we had first observed its arrest following sympathectomy twenty years ago.[15] If treatment is begun before cardiovascular disease has progressed to a severe degree, especially as shown by measurement of renal blood flow or clearance, the chances are good that the disease may at least temporarily be arrested. We prefer to start treatment with hexamethonium, or pentolinium, and possibly add hydralazine and reserpine, later. The diet should contain less than 200 mg. of salt, and digitalis may

be used for heart failure. We prefer to avoid mercurial diuretics during the acute phases of the disease. Diamox has proved occasionally useful to aid in ridding the patient of edema. Chlorpromazine has been of limited value in lessening the nausea often associated with the terminal phase of the disease.

In summary, we believe that current antihypertensive therapy is valuable but that too much must not be expected of it. The advertising claims have in many cases far exceeded the results achieved. Hypertensive cardiovascular disease is still difficult to treat and there will be many failures. Almost none of the drugs are without dangerous side effects and many of them are either ineffective to begin with or become so with use. The drugs are expensive and require in most cases careful dosage regulation by both patient and physician. Withal, however, the long-term outlook for the hypertensive patient seems to me to have vastly improved in the past ten years.

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1
955

REFERENCES

1. Saint-Pierre, H., Corcoran, A. C., Taylor, R. D., and Dustan, H. P.: Relief of Hypotensive Headache by Intravenous Injection of Thiocyanate, J. A. M. A. **152**:493, 1953.
2. Page, I. H.: The Treatment of Arterial Hypertension, Tr. & Stud., Coll. Physicians, Philadelphia **22**:45, 1954.
3. Taylor, R. D., Corcoran, A. C., Dustan, H. P., and Page, I. H.: Further Evaluation of Hydralazine in Treatment of Hypertensive Disease, Arch. Int. Med. **93**:705, 1954.
4. Rowe, G. G., Huston, J. J., Maxwell, G. M., Weinstein, A. B., Tuchman, H., and Crumpton, C. W.: The Effect of 1-Hydrazinophthalazine on Coronary Blood Flow and Cardiac Metabolism in Hypertensive Patients, Proc. 2nd World Congr. Cardiol.,Washington, 1954, Am. Heart Assoc., p. 325.
5. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Controlled Observations on the Effect of Low Salt Dietotherapy in Essential Hypertension, Circulation **3**:1, 1951.
6. Birkhead, N. C., and Allen, E. V.: Comparison of Effects in Hypertension of Hexamethonium and Pentapyrrolidinium Injected Subcutaneously, Proc. Staff Meet., Mayo Clin. **29**:489, 1954.
7. Bhatia, B. B.: On Use of Rauwolfia Serpentina in High Blood Pressure, J. Indian M. A. **11**:262, 1942.
8. Vakil, R. J.: Clinical Trial of Rauwolfia Serpentina in Essential Hypertension, Brit. Heart J. **2**:350, 1949.
9. Corcoran, A. C., Dustan, H. P., Taylor, R. D., and Page, I. H.: Management of Hypertensive Disease, Am. J. Med. **17**:383, 1954.
10. Wilkins, R. W.: Rauwolfia in the Treatment of Essential Hypertension, Am. J. Med. **17**:703, 1954.
11. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Clinical Experience With Reserpine (Serpasil): A Controlled Study, Ann. New York Acad. Sc. **59**:136, 1954.
12. Smirk, F. H.: Action of a New Methonium Compound in Arterial Hypertension, Lancet **1**:457, 1953.
13. Hoobler, S. W.: Treatment of Hypertension, Am. J. Med. **17**:259, 1954.
14. Page, I. H., Corcoran, A. C., Dustan, H. P., and Koppanyi, T.: Cardiovascular Action of Sodium Nitroprusside in Animals and Hypertensive Patients, Circulation **11**:188 (Feb.) 1955.
15. Page, I. H.: Medical Aspects of Surgical Treatment of Hypertension, J. A. M. A. **110**:1161, 1938.
16. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension With Hexamethonium, Circulation **5**:20, 1952.

MANAGEMENT OF THE PATIENT WITH PRIMARY "ESSENTIAL" HYPERTENSION

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VOL
1
195

THE goal in the management of essential hypertension is to prevent or ameliorate manifestations of the disease due to the elevated blood pressure by reducing the pressure, without impairing the blood flow to vital organs.

The underlying cause of essential hypertension is not known, but the immediate cause is an increase in the systemic peripheral resistance to the flow of blood. In uncomplicated hypertension the output of blood by the heart is normal, as are the circulating blood volume and the venous return to the heart.[1] The peripheral resistance is increased, presumably as a result of narrowing of arterioles due to increased sympathetic vasoconstrictor tone, circulating humoral agents which have not been fully identified, and arteriosclerosis. The increased peripheral resistance and blood pressure may be lowered by several means. Sympathetic vasoconstrictor tone may be decreased by reducing central vasoconstrictor activity or by reducing the transmission of impulses across sympathetic ganglia. The former is attempted by sedation, psychotherapy, and by such drugs as the alkaloids of Rauwolfia, veratrum, and ergot. The latter is attempted by ganglionic-blocking drugs (hexamethonium, pentapyrrolidinium) or surgical sympathectomy. Additional means of lowering peripheral resistance and blood pressure are by the administration of direct vasodilator drugs (e.g., hydralazine) and by dietary restriction of sodium.

The precise means employed to attempt to lower the elevated peripheral resistance and blood pressure will depend upon the manifestations and severity of the hypertensive disease. In asymptomatic hypertension, the prognosis is, in general, so good[2] that mild measures are employed which are least likely to produce uncomfortable or deleterious side effects. In patients with manifestations of hypertensive disease attributable to elevation of blood pressure, greater efforts are made to reduce the elevated pressure, but the measures employed and the desirable degree of reduction in pressure may vary. Manifestations of hypertensive disease that appear to be attributable mainly to the elevated blood pressure, such as encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, and left ventricular enlargement and failure, usually warrant efforts to lower the pressure, and will generally improve when this is accomplished. On the other hand, complications of hypertensive disease which

are due primarily to arteriosclerosis and vascular insufficiency, such as cerebral thrombosis, myocardial infarction, retinal vascular occlusion, and nephrosclerosis, will not be benefited by reduction in the blood pressure, and may be made worse if the blood vessels are so fixed that vasodilatation cannot occur and local blood flow is impaired.

A description of the methods employed in the management of patients with hypertensive disease, and the results of such management, will be presented. Except where otherwise indicated, specific patients or groups of patients referred to were studied in The Johns Hopkins Hospital. Earlier results of this study have been previously reported.[3,4]

Methods of Reducing Elevated Blood Pressure

ANTIHYPERTENSIVE DRUGS

Rauwolfia.—Mechanism of action: Alkaloids derived from this plant are believed to reduce the activity of the sympathetic vasoconstrictor center and of other sympathetic centers. They also have a mild sedative effect, which lessens anxiety.

Indications and contraindications: Rauwolfia may be administered alone to patients with asymptomatic or mild hypertensive disease, or it may be administered to patients with moderate or severe hypertensive disease as an adjunct to more potent drugs such as the methonium or veratrum compounds, or hydralazine. When Rauwolfia is used as an adjunct to more potent antihypertensive drugs, the effect is usually additive, or slightly more, and the dose of these drugs may usually be reduced, with resulting reduction in their side effects. In some instances it has been possible to discontinue the more potent drug after several months of reduction of blood pressure by the combination, continuing Rauwolfia alone. Two of the side effects of Rauwolfia are opposite to those of drugs with which it is frequently combined. The bradycardic effect of Rauwolfia may offset the tachycardia of hydralazine, and the gastrointestinal-stimulating effect of Rauwolfia may help combat the constipation produced by the methonium compounds. There are no specific contraindications to Rauwolfia.

Dose: Rauwolfia is administered orally one to four times a day, either as the crude root (100 to 400 mg. a day), or as the purified alkaloid, reserpine (0.1 to 0.7 mg. a day).

Effect on blood pressure: Rauwolfia is a generally mild antihypertensive drug which is slow in onset of action, and which has its greatest effect in patients with mild, labile hypertension.[5,6] In patients with more severe hypertension the reduction in blood pressure is slight or moderate. Rauwolfia usually does not reduce the pressure by more than 30 mm. Hg systolic and 20 mm. diastolic, regardless of the initial level of pressure, and the average reduction is about one-half this. It is evident that in patients with severe hypertension Rauwolfia alone does not have adequate antihypertensive effect, but must be used as an adjunct to more potent drugs.

Side effects: Bradycardia, mild sedation, and nasal congestion usually occur, but are seldom troublesome. Occasionally there may be nosebleeds, presumably

owing to turbinate vasodilatation, nausea, vomiting, diarrhea, nightmares, drowsiness, and rarely decreased libido and postural hypotension. There is not infrequently increased appetite and gain in weight, which may be troublesome in patients who are already obese. The mild sedation is frequently a helpful side effect, but may occasionally be accompanied by slowing of thinking and some diminution of mental acuity and judgment.

Ganglionic-blocking Agents (Methonium Compounds: Hexamethonium and Pentapyrrolidinium [Ansolysen]).—Mechanism of action: These compounds are capable of blocking the transmission of nervous impulses across autonomic ganglia, both sympathetic and parasympathetic. Since sympathetic vasoconstrictor tone makes a significant contribution, of varying degree, to the elevation of blood pressure in hypertensive subjects, ganglionic blockade results in reduction in pressure. Since sympathetic vasoconstrictor tone is essential for the maintenance of the blood pressure in the erect position, ganglionic blockade also produces postural hypotension. The decrease in vasomotor tone may result in pooling of blood in the periphery and decrease in venous return and cardiac output.[4] This occurs after rapid reduction in pressure when the patient is recumbent, and is more marked on standing. The dose of methonium compound that produces postural hypotension is less than that required to lower the recumbent pressure, and the largest doses are required to inhibit the pressor effects of cold, pain, or emotion.[7]

Indications and contraindications: Methonium compounds may be administered intravenously or intramuscularly when rapid reduction of blood pressure is desired, as in severe encephalopathy, but the usual route is oral. They are administered to patients with labile hypertension and mild symptoms only when Rauwolfia alone has proved inadequate. Their main usefulness is in patients with moderate or severe sustained hypertension, with cerebral or cardiac symptoms, or in the malignant phase. Rauwolfia is generally administered concomitantly. Since rapid reduction in pressure by methonium compounds may result in reduction in cardiac output, particularly during postural hypotension, these compounds may produce harmful effects when there is clinical evidence of severe reduction in blood flow to any of the vital organs. They are contraindicated in patients with recent myocardial infarction or cerebral thrombosis, and must be used with caution, if at all, in patients with renal insufficiency.

Dose: Hexamethonium may be injected intravenously at the rate of 1 to 3 mg. per minute until the blood pressure is reduced to the desired level. The average intravenous dose required to lower the blood pressure to or near normotensive levels in fifty patients was 42 mg. The subcutaneous or intramuscular dose is initially 5 mg. three times daily, increased by increments of 5 mg., if necessary to as high as 75 mg. three times a day. The oral dose is initially 125 mg. three times a day before meals, increased daily as needed by increments of 125 mg. each dose. *Pentapyrrolidinium* is administered in doses one-fifth those of hexamethonium.

Effect on blood pressure: Intravenous methonium compound will lower the recumbent blood pressure of nearly all hypertensive patients to or near normal

and produce marked postural hypotension. Of fifty patients, only two failed to have a moderate reduction in the recumbent pressure.[3] Intramuscular or oral administration usually produces a moderate reduction in recumbent pressure, and further reduction on standing to or near normotensive levels.[3,8-11] The initial regulation of dose is best carried out in the hospital, unless repeated observations of blood pressure can be made in the office or dispensary over a period of several hours each day. The home recording of blood pressure, in suitable patients, facilitates subsequent adjustments of dose.[12] Patients are advised to sleep with the head of the bed elevated, in order to take advantage of postural reduction in pressure, and to reduce or omit the next dose of drug when giddiness occurs on quiet standing.[8] The effective dose varies considerably, and cannot be predicted from the response to sodium amytal-induced sleep, or by other means. The dose of drug must be gradually increased at intervals of one or more days until the standing pressure is normal, or near normal. At this dose the recumbent pressure will usually be intermediate between the original and normotensive levels, although it may be only slightly reduced in some patients. The optimal dose of drug is determined, in ambulatory patients, by the blood pressure during standing, rather than recumbency, since attempts to lower the latter uniformly to normotensive levels usually result in excessive postural hypotension. In a group of seventy patients an average daily dose of 1.3 Gm. of hexamethonium or 260 mg. of pentapyrrolidinium reduced the standing blood pressure to or near normal, and lowered the recumbent pressure from an average of 215/125 to 175/105. During the first few weeks of drug administration some degree of "tolerance" developed, particularly to hexamethonium. The dose of hexamethonium had to be increased threefold, and that of pentapyrrolidinium by one-half, in order to maintain reduction in pressure. After several weeks or months of maintenance of reduced pressure, however, the dose could frequently be lowered, and when the methonium compound was administered concomitant with Rauwolfia or hydralazine, it could occasionally be considerably reduced in dose or even discontinued.

Most patients receiving methonium have considerable fluctuations in blood pressure, both recumbent and erect, not always correlated with the time of drug administration. They require frequent adjustment of dose, particularly during the first few weeks. Postural hypotension tends to become less marked after prolonged drug administration, but may increase at any time, especially during warm weather and following exercise. Emotional tension tends to increase the blood pressure and drug requirement, while relaxation has the opposite effect. Some patients regularly reduce their dose over week ends.

Regulation of blood pressure by oral hexamethonium alone was unsatisfactory in most patients over prolonged periods of time because of the development of tolerance and the necessity of giving large doses which sometimes diminished intestinal motility. The concurrent administration of hydralazine enabled smaller doses of hexamethonium to be administered, decreased the degree of tolerance, and produced moderate reduction of pressure over prolonged periods in over one-half the patients.[3,13] The concurrent administration of Rauwolfia with hexamethonium has similar effects.

Pentapyrrolidinium not only has somewhat longer duration of action than hexamethonium, but the development of tolerance is slower and less marked.[9,14] Because of this, and because there is less tendency to decreased intestinal motility, pentapyrrolidinium has proved to be more satisfactory than hexamethonium, although it, too, produces wide variations in both the recumbent pressure and degree of postural hypotension. The effect of either compound is increased by low sodium intake or low serum sodium concentration, and following hypertensive encephalopathy or cerebral vascular accident.[3]

Side effects: In most patients there is blurring of vision and constipation. In some there is also increased temperature of the extremities, sometimes associated with chilly sensations, anorexia, gastric dilatation, transient nausea and vomiting, and urinary hesitancy. These side effects usually diminish with continued administration of drug, but frequently pilocarpine is administered orally (5 to 15 mg.) or locally to relieve blurring of vision, and laxatives, enemas, and oral prostigmine (15 to 30 mg.) to relieve constipation. In rare instances obstipation, fecal impaction, or paralytic ileus may occur and require cessation of methonium administration and appropriate treatment. In some patients there may be impotence, drowsiness, lethargy, and subjective weakness. Fatal pulmonary fibrosis has been reported.[15] Constipation is generally less marked following pentapyrrolidinium than hexamethonium, but blurring of vision is more troublesome. Since the methonium compounds inhibit reflex increases in vasomotor tone they produce increased susceptibility to the hypotensive effect of paralytic ileus, blood loss, and sodium depletion. One patient developed fatal shock following paralytic ileus induced by hexamethonium.

Hydralazine (1-Hydrazinophthalazine, Apresoline).—Mechanism of action: Although early observations indicated an action primarily on the central vasoconstrictor center, more recent studies have pointed to a vasodilator action, especially in the splanchnic and renal areas.[16,17] This vasodilatation causes, or is accompanied by, an increase in venous return to the heart, stroke output, and cardiac rate and output.[16]

Route and dose: The intravenous and intramuscular dose is 10 to 20 mg., repeated at intervals of one-half hour or longer until the desired reduction in pressure is attained. The hypotensive effect begins ten minutes after intravenous injection and is maximal twenty minutes later. Oral hydralazine is administered in an initial dose of 10 to 25 mg. four times a day, and the dose progressively increased by increments of 25 to 50 mg. a day until the desired reduction in blood pressure is attained, or until the occurrence of uncomfortable side effects prevents further increase.[18] The average daily dose administered was 350 mg. As the dose was increased above 200 mg. a day the incidence of side effects increased, although a few patients could tolerate as much as 1,000 mg. a day.[3]

Indications and contraindications: Intravenous hydralazine is of particular value when rapid reduction in blood pressure is indicated, as in severe encephalopathy. It may also be used in the management of the encephalopathy of toxemia of pregnancy, since reduction in pressure by hydralazine is less likely to injure

VOL. 1 1955

the fetus than is reduction by methonium compounds.[19] Since oral hydralazine produces a high incidence of uncomfortable side effects, and occasionally results in a rheumatoid or lupuslike syndrome after prolonged administration,[20-24] its use should probably be limited to those patients who require an adjunct to Rauwolfia and methonium for adequate regulation of pressure, and to patients who require reduction in pressure despite the presence of renal insufficiency. Hydralazine is less likely to decrease renal blood flow and function than methonium or veratrum compounds, and may be administered with these compounds, when necessary, to diminish their renal effects.[25] Hydralazine should be used with caution, if at all, in patients with angina or cardiac failure, since it increases cardiac rate, output, and work load.

Effect on blood pressure: In contrast to the methonium compounds, hydralazine, administered intravenously, produced a greater reduction in pressure in patients who were not in the malignant phase of hypertension and who had normal blood nonprotein nitrogen levels. An average of 29 mg., administered in doses of 10 to 20 mg. at one-half-hour intervals, lowered the pressure from an average of 210/121 to 121/67 mm. Hg in ten of these patients, while 62 mg. lowered the pressure from 230/141 to 191/111 mm. Hg in ten patients with malignant hypertension and renal insufficiency. This difference in response may be due to the vascular tree being more fixed and difficult to dilate in the latter group. Orally administered hydralazine, in average daily dose of 300 mg., produced a moderate reduction in blood pressure in one-half of a group of sixty patients to levels intermediate between the original and normotensive, and no more than a slight transient reduction in the other half. In patients with benign hypertension the blood pressure fell from an average of 212/129 to 183/109, and in patients with malignant hypertension from 235/142 to 198/120. None of the patients had postural hypotension. There was no correlation with the reduction in blood pressure that occurred during sodium amytal–induced sleep. The effect of hydralazine on the blood pressure diminished to some extent over a period of several months, but this development of tolerance was generally not marked. Hydralazine produced slight to moderate cardioacceleration, even in some of the patients who had little or no fall in blood pressure, the average rate increasing from 86 to 97 per minute, and on standing to 110 per minute.

Side effects: In one-third of the patients studied, hydralazine had to be discontinued or reduced in dose because of the occurrence of side effects. These included, in order of frequency, headache, pain in back of the neck, shoulders, and arms, malaise, rhinitis, conjunctivitis, lacrimation, photophobia, periorbital edema, hiccups, giddiness in absence of fall in blood pressure, substernal discomfort in absence of fall in blood pressure, nausea, diarrhea, and fever. In two patients angina pectoris, and in two others myocardial infarction, occurred following reduction in pressure. In about 10 per cent of the patients a slight reduction in the hematocrit occurred, probably because of hemodilution.

Two patients, of thirty who received hydralazine in doses exceeding 300 mg. a day for more than one year, developed arthralgia, followed by migratory arthritis, with hot, swollen, and painful joints. In one of the patients, who had received 400 mg. of hydralazine daily for two years, this was followed by fever,

malaise, lymphadenopathy, chest pain, pericarditis with effusion, and the appearance of elevated serum globulin, abnormal liver function tests, and lupus erythematosus cells in the peripheral blood. These signs and symptoms gradually disappeared when hydralazine was discontinued. The reported incidence of this rheumatoid or lupuslike syndrome following prolonged administration of hydralazine has been 8 to 11 per cent.[20,21] Additional manifestations have included facial eruption, subcutaneous nodules, anemia, leukopenia, and transiently positive serologic test for syphilis. The reported instances of this syndrome began after administration of the drug in doses exceeding 300 mg. a day for more than eight months. In no instance was the drug promptly stopped following the earliest occurrence of arthralgia. Restriction of hydralazine administration to a daily dose of less than 300 mg. and to a period of less than eight months, and prompt discontinuation of the drug following the earliest appearance of arthralgia, should reduce the incidence of this drug toxicity or hypersensitivity.

Veratrum Alkaloids.—Protoveratrine may be administered intravenously at the rate of 1 μg per kilogram per minute to patients with severe encephalopathy, including those with toxemia of pregnancy.[26] Protoveratrine may also be administered orally, usually in dose of 1 mg. twice a day.[27] Crude preparations of veratrum (e.g., Veriloid) may be administered orally, usually in doses of 9 to 15 mg. a day.[28] The veratrum alkaloids decrease central vasoconstrictor tone by increasing afferent stimuli from the carotid sinus and aortic and coronary receptors. Unfortunately there is usually associated stimulation of the vomiting center, so that doses required to reduce the blood pressure frequently also produce nausea and vomiting. For this reason, other antihypertensive drugs have usually been tried first, unless there was some contraindication to their use. In some patients in whom the methonium compounds did not produce the desired reduction in pressure, or in whom these compounds were undesirable because of renal insufficiency, veratrum alkaloids produced a slight to moderate reduction in pressure.

DIETARY MANAGEMENT

Aside from weight reduction in obese patients, dietary management of hypertension depends upon rigid restriction of sodium intake. The value of low-cholesterol and low-fat diets in the prevention of atherosclerosis is not yet proved. In order to achieve reduction in blood pressure by salt restriction alone the daily intake of sodium must be below 500 mg., and preferably below 200 mg.[29] The mechanism by which depletion of body sodium may lower elevated blood pressure is not known. There appears to be no virtue to restriction of other food constituents, and no advantage of the rice diet over other diets of equally low sodium content. Cationic-exchange resins administered in doses of 20 Gm. three times a day reduce the gastrointestinal absorption of sodium, usually by about 50 per cent.[30] These may be used as a supplement to dietary restriction of sodium, but if the diet is not already low in sodium the exchange resins alone will be ineffective. Most patients prefer additional sodium restriction to the exchange resins. Successful dietary restriction of sodium may produce appreciable reduction in blood pressure in up to a fourth of patients who

VOL. 1 1955

adhere to the dietary regime. However, successful dietary restriction is difficult and occasionally results in the "low-salt syndrome," especially in those patients with renal insufficiency who are unable to conserve sodium. Less rigid salt restriction is sometimes useful as an adjunct to the antihypertensive drugs. The effect of methonium compounds may be enhanced and the development of tolerance delayed by restriction of sodium intake to 1 or 2 Gm. a day.[3,8]

SURGICAL SYMPATHECTOMY

This usually results in a reduction in recumbent blood pressure and postural hypotension, but the recumbent pressure returns in most instances to or near the original level within about eight months. Postural hypotension and relief of manifestations of elevated blood pressure may persist for a longer period of time. In a small proportion of patients permanent remission of hypertension occurs.[31] There is unfortunately no way of predicting which patients will experience permanent remission or have prolonged reduction in pressure. There is no correlation between the effect of methonium compounds and of sympathectomy on the blood pressure.[3,7] The frequency with which sympathectomy is performed in the management of hypertension has decreased sharply since the advent of antihypertensive drugs. In view of the difficulty of predicting the long-term effects of sympathectomy, and the morbidity of the operative procedure, it would appear to be reasonable to attempt to control the blood pressure by antihypertensive drugs and sodium restriction before attempting sympathectomy. In those patients in whom a thorough trial of antihypertensive drugs, supplemented if necessary by salt restriction, does not control the blood pressure and manifestations due to elevated pressure, sympathectomy would appear to be warranted, unless there is some contraindication. Following sympathectomy there is usually an increase in response to methonium compounds and to salt restriction, even when the sympathectomy has not resulted in a reduction in pressure.[3] Since reduction in pressure by sympathectomy may result in reduced renal blood flow, the presence of renal insufficiency with blood nonprotein nitrogen elevated above 60 mg. per cent is a contraindication to surgical sympathectomy. Reduction in blood flow to other vital organs may also occur in the presence of marked arteriosclerosis, so that a recent cerebral vascular accident, recent myocardial infarction, or severe angina pectoris is also a contraindication to this procedure.

SUGGESTED SEQUENCE OF ANTIHYPERTENSIVE MEASURES

When severe encephalopathy requires rapid reduction in blood pressure, intravenously administered hydralazine, methonium, or protoveratrine may be employed. When orally administered drugs are employed, this would usually begin with Rauwolfia. When Rauwolfia alone is ineffective, as is usually the case in moderate or severe hypertensive disease, pentapyrrolidinium may be added. If the recumbent blood pressure cannot be moderately reduced without excessive postural hypotension, or if the side effects of the required dose are prohibitive,

hydralazine may be added, in a daily dose of less than 300 mg. and for a period of less than eight months. During this time it is often possible to reduce the dose of pentapyrrolidinium. If these measures are unsuccessful veratrum compounds may be substituted for the latter drug.

When the blood pressure is adequately reduced by doses of antihypertensive drugs that do not produce prohibitive postural hypotension or side effects, a daily dietary sodium intake of as much as 4 Gm. may usually be permitted, unless cardiac failure is present. Higher salt intake is not encouraged unless there is excessive salt loss due to renal insufficiency. If the blood pressure is not controlled by well-tolerated doses of antihypertensive drugs, more rigid salt restriction (200 mg. to 2 Gm.) may be instituted. In very cooperative patients rigid salt restriction (200 mg.) may be attempted even before drug administration. When these measures do not meet with success, either because of lack of effect or lack of cooperation, surgical sympathectomy would seem to be warranted, unless there is a contraindication to this procedure. If the blood pressure is not adequately reduced following sympathectomy, antihypertensive drugs and salt restriction may be resumed.

VOL 1 195

Management of the Stages and Complications of Essential Hypertension

DIAGNOSIS OF ESSENTIAL HYPERTENSION

This is established by excluding other causes of hypertension, such as primary or occlusive-vascular renal disease (bilateral or unilateral), coarctation of the aorta, pheochromocytoma. Cushing's disease, cerebral lesions (mid-brain, brain stem, increased intracranial pressure), lead poisoning, and acute porphyria.

ASYMPTOMATIC ESSENTIAL HYPERTENSION

The prognosis in this group of patients is so good, particularly in patients whose diastolic blood pressure is usually below 120 mm. Hg,[2] that only those treatment measures seem justifiable which are without hazard and which do not interfere with the mental or physical well-being of the patient. Such measures include reassurance, weight reduction if obesity is present, mild sedation with phenobarbital, and psychotherapy if needed. It is not yet known whether reduction in the blood pressure of patients in this group will prevent or retard the onset of malignant hypertension or of the various complications of arteriosclerotic hypertensive disease. Studies designed to answer this question are in progress, but it will be many years before it will be answered. Meanwhile it does not seem warranted to employ the more potent antihypertensive drugs, which are not without discomforting side effects, or to employ rigid dietary restriction of sodium or sympathectomy in the management of these patients. However, the administration of Rauwolfia would not seem unreasonable, provided that it produces no appreciable discomfort. Yearly examinations are warranted so that the earliest manifestations of progression of the disease may be detected and further treatment instituted. In those patients with asymptomatic hypertension whose diastolic pressure is frequently above 120 mm. Hg,

it would appear reasonable to add additional antihypertensive drugs to the regimen if the pressure is not lowered by Rauwolfia alone, in order to reduce left heart strain and the possibility of cerebral hemorrhage. Orally administered pentapyrrolidinium or veratrum may be used for this purpose if the effective dose does not produce uncomfortable side effects, and salt restriction may be added if necessary.

ESSENTIAL HYPERTENSION WITH SYMPTOMS ATTRIBUTABLE TO ELEVATION OF BLOOD PRESSURE

The manifestations of hypertensive disease which appear to be attributable mainly to elevation of blood pressure include most of the familiar central neural, retinal, and cardiac manifestations of the disease, as well as hemorrhage from the nose or occasionally from other areas. Similar manifestations may result in part or in the main from vascular sclerosis or spasm, and it is frequently important to attempt to assess the role of the hypertension and of the vascular disease, since reduction in pressure will usually improve manifestations of the disease due to the former, but may make those due to the latter worse.

Central Neural Manifestations.—The manifestations of hypertensive disease which are most frequently and dramatically improved following reduction in pressure are headache, dizziness, vertigo, and encephalopathy. The latter is indicated by severe headache, often nausea and vomiting, drowsiness, disorientation, papilledema, syncope, aphasia, paresthesias, and in the most severe form amaurosis, transient paralyses, convulsions, and coma. The means employed to attempt to reduce the pressure will depend upon the severity of symptoms, and the presence or absence of contraindications to the use of various measures. When the symptoms are limited to persistent headache or giddy spells, time will usually permit a trial on Rauwolfia. If this is unsuccessful in lowering the pressure and relieving symptoms, or if more rapid effect is desired, pentapyrrolidinium may be added. If this drug is without effect, or if effective doses are not tolerated, salt restriction or hydralazine (for short periods of time) may be added, or veratrum alkaloid substituted. If the encephalopathy is severe, hydralazine, hexamethonium, or protoveratrine may be administered intravenously. None of these drugs increases cerebral blood flow, but blood flow may be maintained following reduction in pressure,[32] unless the reduction is excessive or arteriosclerosis prevents adequate vasodilatation. Following control of the acute episode, the patient may be begun on oral administration of these drugs, supplemented by Rauwolfia. Sedatives may be employed, as needed, but depression of the respiratory center must be avoided.

In some patients, particularly those with severe arteriosclerosis or malignant hypertension, the cerebral vessels are apparently unable to dilate adequately following reduction in pressure, limiting the degree of improvement following reduction in pressure, and even resulting in a decrease in cerebral blood flow and worsening of cerebral symptoms, particularly syncope. This is most likely to occur following rapid or excessive reduction in pressure by intravenous administration of antihypertensive drugs, but may also occur following oral ad-

ministration. The antihypertensive drug must be temporarily discontinued until the symptoms suggestive of excessive reduction of cerebral blood flow disappear, following which drug administration may be resumed at a reduced dosage level.

Cerebral or subarachnoid hemorrhage is an indication for prompt reduction in blood pressure, while recent cerebral thrombosis is a contraindication. In a patient who has had a cerebral vascular accident, it is sometimes extremely difficult to tell whether this is the result of thrombosis or hemorrhage. In patients with mild hypertension the majority of cerebral vascular accidents, perhaps 80 per cent, are due to arteriosclerosis, with vascular insufficiency or thrombosis leading to infarction. In patients with severe hypertension, it is probable that about one half are due to vascular insufficiency or thrombosis and one half to hemorrhage. A gradual, fluctuating onset of weakness and absence of other signs of encephalopathy suggest vascular insufficiency or thrombosis, while apoplectic onset accompanied by other manifestations of encephalopathy indicates hemorrhage. Grossly bloody spinal fluid nearly always indicates hemorrhage, but clear fluid does not exclude an intracerebral hemorrhage with hematoma. If the cause of the cerebral vascular accident is not clear, the blood pressure may be cautiously reduced and the effect on the patient's mental state and symptoms observed. An increase in confusion or an extension of the signs of cerebral vascular accident calls for discontinuation of antihypertensive medication, while improvement warrants further cautious reduction in blood pressure.

Retinopathy.—Papilledema, hemorrhages, associated visual impairment, and to a lesser degree exudates generally improve following reduction in the blood pressure. As in patients with hypertensive encephalopathy, the degree of improvement may be limited by the presence of fixed vascular change, and rapid or excessive reduction in pressure may result in diminution or loss of vision, particularly in patients with malignant hypertension or retinal vascular occlusion. This occurred in four patients out of 100 whose pressure was moderately reduced by antihypertensive drugs, but vision returned when the pressure was allowed to rise.

Cardiac Manifestations.—In the treatment of cardiac failure the physician relies mainly on digitalis, salt restriction, diuretics (mercurial and Diamox), and, in severe pulmonary edema, oxygen, tourniquets, and venesection. In hypertensive patients with left ventricular enlargement and failure, without evidence of severe myocardial insufficiency, reduction in blood pressure is also usually of some benefit, and may result in additional improvement in palpitation, dyspnea, orthopnea, recurring pulmonary edema, gallop rhythm, and, after several weeks, in heart size. Manifestations of right heart failure may occasionally improve slightly. Angina pectoris may improve in some patients, and get worse in others, depending on the degree and rate of reduction in pressure and on the effect of this reduction on coronary blood flow.[3,4] Abnormalities in the electrocardiogram and ballistocardiogram attributable to hypertension usually improve after gradual reduction in pressure, and may improve or become worse after rapid reduction.[4]

Cardiac manifestations which improve after reduction in pressure appear to be those attributable mainly to hypertension and increased left ventricular work and strain. The improvement is considered to be due to a decrease in work load of the left ventricle,[4] and perhaps in venous overloading of the left ventricle following vasodilatation and diversion of blood from the central to the peripheral vascular tree.[33] On the other hand, manifestations attributable to insufficient coronary blood flow may become worse after reduction in pressure, particularly if this is rapid or excessive, and particularly in patients with severe arteriosclerosis or malignant hypertension. These include cardiac failure due to myocardial insufficiency, coronary insufficiency, and frequently angina. Of 100 patients in whom the blood pressure was moderately reduced by antihypertensive drugs, four developed symptoms and electrocardiographic evidence of myocardial infarction, which was fatal in one. History or electrocardiographic evidence of myocardial infarction or of severe coronary insufficiency is a contraindication to reduction in pressure. When there is mild angina, or when the role of myocardial insufficiency in cardiac failure cannot be evaluated, any reduction in pressure should be carried out with caution and with periodic electrocardiographic evaluation. Since hydralazine increases cardiac rate, output, and work it is contraindicated in patients with angina or electrocardiographic evidence of coronary insufficiency. Methonium or veratrum compounds, supplemented by Rauwolfia, would appear to be preferable in patients with cardiac failure, but the concomitant administration of hydralazine has not prevented improvement.[3] The fact that these drugs have opposing effects on cardiac output may be relevant.

Rapid reduction in pressure by methonium or veratrum compounds or by hydralazine may result in decreased excretion of salt and water.[4,25,34] However, this is usually of short duration, and has not resulted in increased edema or cardiac failure.

Nephrosclerosis.—There is no measure known to reverse nephrosclerosis, or to delay its progression. Management of this complication is limited to efforts to ameliorate the effects of renal insufficiency. When the blood nonprotein nitrogen is elevated, protein intake should be sufficiently restricted to prevent further increase, usually to 0.5 Gm. per kilogram ideal body weight per day, plus an amount corresponding to that lost in the urine. The fluid intake should be adequate to produce a urinary output of 2 to 3 L. a day, unless this results in edema and weight gain.

Renal insufficiency may result in excessive depletion or retention of sodium and potassium, lowering of serum calcium due to phosphorus retention, and acidosis. Sodium depletion, which is accelerated by dietary restriction of this ion, may result in a critical decrease in plasma, extracellular and intracellular fluid volume, and in the "low-salt" syndrome. This is characterized by decreased renal blood flow, increased renal insufficiency, muscle aches and cramps, headache, and even circulatory collapse. Replacement of sodium by orally or parenterally administered sodium chloride may improve renal function appreciably by increasing renal blood flow, and will relieve the other manifestations of the "low-salt" syndrome. However, the administration of excessive amounts

of sodium must be avoided, lest the resulting expansion of plasma volume lead to, or accentuate, cardiac failure. When sodium depletion is accompanied by acidosis, due to excess cation loss and to retention of acid products of protein and fat metabolism, sodium bicarbonate, citrate, or lactate should be administered in place of sodium chloride. Vomiting, with resultant dehydration, salt loss, starvation, increased catabolism of protein and fat and increased nitrogen retention, calls for intravenous administration of sodium chloride and lactate, 10 per cent glucose, and vitamins. Chlorpromazine (Thorazine), administered in doses of 25 to 50 mg. four times a day orally or parenterally, frequently diminishes nausea and vomiting.

Retention of potassium may lead to hyperkalemia, and, less frequently, excessive urinary loss to hypokalemia, each resulting in electrocardiographic changes and muscular weakness, and calling for dietary restriction or supplementation. Phosphate retention leads to hypocalcemia, but hypocalcemic tetany may be inhibited by concomitant acidosis, which makes available more ionized calcium. Tetany is not infrequently induced when sodium bicarbonate, citrate, or lactate is administered to correct the acidosis. Administration of calcium gluconate or lactate orally or intravenously will prevent or ameliorate hypocalcemic tetany. Low-phosphorus diet, with aluminum hydroxide gel, may reduce the serum phosphorus level.

Since anemia may decrease renal blood flow and filtration rate,[35] reduction in the hematocrit below 25 per cent warrants the transfusion of blood, or, in patients with lowered cardiac reserve, of washed red blood cells suspended in glucose.

Renal insufficiency is never improved by reduction in blood pressure, and is sometimes made worse, particularly following rapid or excessive reduction.[3,4,25] In patients with nephrosclerosis, particularly those in the malignant stage, the renal vascular tree appears to be fixed and does not dilate following reduction in pressure. Renal insufficiency is not, however, a contraindication to cautious reduction in pressure when this is warranted by severe encephalopathy or left heart failure. Since methonium and veratrum compounds produce a temporary diminution in renal blood flow and glomerular filtration rate following rapid reduction in pressure,[4,34] these drugs should not be administered alone to patients with renal insufficiency. Hydralazine is much less likely to reduce renal blood flow and filtration rate[16,25] and is therefore preferable in these patients. Unfortunately the hypotensive effect of hydralazine is less marked in patients with renal insufficiency than in patients with good renal function, so that, when administered alone, it seldom produces an appreciable reduction in pressure. It may, however, be administered concomitant with methonium or veratrum compounds. Rapid deterioration of renal function was not observed following gradual reduction in pressure by hexamethonium and hydralazine, but did occur in four patients following hexamethonium alone. In these patients the renal insufficiency progressed despite prompt discontinuation of the drug and restoration of elevated blood pressure, and terminated in uremia.[3,4]

While hydralazine produced an 80 per cent increase in renal blood flow in five hypertensive patients with normal blood nonprotein nitrogen following

intravenous administration, and a 65 per cent increase following oral administration, it produced no change in renal blood flow in five other patients with elevated blood nonprotein nitrogen, indicating failure of renal vasodilatation to occur in these patients.[25] In no instance did hydralazine increase glomerular filtration rate or renal function, or appear to retard the progression of renal insufficiency; in fact, when the blood pressure was reduced below normal a decrease in renal blood flow and filtration rate occurred until the blood pressure was restored. However, the prior administration of hydralazine did result in less marked depression of renal blood flow and filtration rate following reduction in blood pressure by hexamethonium than occurred when the latter drug was administered alone. Nevertheless, in patients with renal insufficiency in whom reduction in blood pressure is attempted, by hydralazine administered alone or with methonium or veratrum compounds, the pressure must be reduced with great caution, with frequent determination of blood nonprotein nitrogen, and stabilization of the blood pressure at a level which does not result in increased nitrogen retention.

VOL.
1
1955

Malignant Hypertension.—This stage of the disease, characterized by sustained marked elevation of the diastolic blood pressure, with papilledema, and later encephalopathy and rapidly progressive renal insufficiency, warrants attempts to reduce the blood pressure, unless specific contraindications are present, such as severe coronary artery disease, recent myocardial infarction, or cerebral thrombosis. In the presence of renal insufficiency the pressure must be reduced cautiously, with frequent determination of nonprotein nitrogen. Patients with malignant hypertension are usually initially more responsive to the hypotensive effect of methonium compounds than are patients who are not in the malignant phase, and they are usually less responsive to hydralazine. Nevertheless, hydralazine should probably be administered concomitant with methonium or veratrum compounds in order to diminish the likelihood of decreased renal blood flow and function following reduction in pressure. As in patients who are not in the malignant phase, reduction in pressure usually results in amelioration of manifestations due mainly to elevated pressure, such as encephalopathy, retinopathy, and left ventricular strain, and no improvement in those due mainly to vascular sclerosis or necrosis, such as renal insufficiency. Patients in the malignant phase are more susceptible to the harmful effects of rapid or excessive reduction in pressure, presumably because of a more fixed vascular tree which prevents vasodilatation and maintenance of blood flow to the vital organs following reduction in pressure. The most common untoward effect of reduction in pressure has been increased renal insufficiency, but myocardial infarction, angina, cerebral thrombosis, and amaurosis have also occurred.[3] In most instances it has been either not possible or not desirable to reduce the recumbent blood pressure below levels intermediate between the original level and normal tension. In twenty patients with malignant hypertension the administration of hydralazine with hexamethonium or pentapyrrolidinium resulted in a reduction in the recumbent pressure from an average of 235/145 to 185/110 mm. Hg in fourteen over a period of several months, and a further reduction in the standing pressure. In six patients only transient reduction

in recumbent pressure was attained. In all but two of the patients in whom moderate reduction in pressure was achieved, the manifestations of encephalopathy improved within a few days. Papilledema, retinal hemorrhages, and manifestations of left ventricular decompensation improved in over one-half. Renal function improved in none, and the progression of renal insufficiency did not seem to be impeded. In one patient fatal myocardial infarction occurred after reduction in pressure to near normal levels, and in two temporary blindness occurred. Most of the patients have died of renal insufficiency, three of cerebral hemorrhage or thrombosis, and one of cardiac failure. Most of the patients were improved symptomatically during life, but it is not certain that their life was significantly prolonged. On the other hand, three patients who have maintained good renal function are alive and in good condition three years after the onset of severe hypertension, papilledema, and encephalopathy, and it is likely that their life has been prolonged.

VOL. 1 1955

TREATMENT OF EXCESSIVE REDUCTION IN BLOOD PRESSURE

If the blood pressure does not begin to return toward well-tolerated levels when the foot of the bed is elevated, Ace bandages may be applied to the legs and pressor drugs administered. The most potent of these is noradrenaline (Levophed), which is administered intravenously by drip at the rate of 4 to 10 μg per minute. If the excessive reduction in pressure is due to methonium compound, noradrenaline may produce an overshoot of the blood pressure to very high levels, because of inhibition of reflexes concerned with stabilization of blood pressure. The administration of the pressor drug may have to be continued for several hours before stabilization of blood pressure occurs. When the reduction in pressure has not been too severe, methoxamine (Vasoxyl[36] 15 to 25 mg. intramuscularly) or Neo-synephrine (2 to 4 mg. intramuscularly) may be employed. Following excessive reduction in blood pressure an electrocardiogram should be obtained to ascertain if the fall in pressure was due in part to myocardial infarction, or if this occurred while the pressure was low.

CONCLUSIONS

Administration of antihypertensive drugs, supplemented by salt restriction when necessary, is capable of reducing the blood pressure in a large majority of patients with hypertensive disease. In most patients with severe hypertension the recumbent pressure can be reduced over prolonged periods only to levels intermediate between the original pressure and normal tension, while the standing pressure will usually be further reduced in patients receiving methonium compounds. Prolonged reduction in pressure by drugs does not result in disappearance of the hypertensive disease, as occasionally occurs after sympathectomy, although the amount of drug needed may often be reduced. Manifestations of hypertensive disease due mainly to elevated pressure, such as encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, left ventricular failure, and occasionally angina, are usually improved following even moderate reduction in pressure, and it is likely that life has been prolonged in some patients

as a result. Manifestations due mainly to vascular sclerosis or necrosis, on the other hand, are not improved and may become worse following reduction in pressure, particularly in patients with severe arteriosclerosis or malignant hypertension. These include renal insufficiency, cerebral thrombosis or vascular insufficiency, retinal occlusion, and coronary insufficiency. While patients who are not in the malignant phase of hypertension are usually improved following reduction in pressure, it is still too early to ascertain if this will delay the progression of vascular disease and onset of complications due to vascular disease, such as nephrosclerosis, and of malignant hypertension, or greatly prolong life. In the majority of patients with malignant hypertension, moderate reduction in pressure did not appear to delay the progression of renal insufficiency or prolong life, although many of the other manifestations of the disease were improved. However, in some patients who maintained good renal function, there was not only improvement in encephalopathy and left ventricular failure, but there was also very likely prolongation of life.

REFERENCES

1. Goldring, W., and Chassis, H.: Hypertension and Hypertensive Diseases, New York, 1944, The Commonwealth Fund.
2. Perera, G. A.: Hypertensive Vascular Disease; Description and Natural History, J. Chron. Dis. **1**:33, 1955.
3. Grob, D., and Langford, H. G.: Further Observations on the Effects of Autonomic Blocking Agents in Patients With Hypertension. I. General Systemic Effects of Hexamethonium, Pentamethonium, and Hydrazinophthalazine, Circulation **8**:205, 1953.
4. Grob, D., Scarborough, W. R., Kattus, A. A., Jr., and Langford, H. G.: Further Observations on the Effects of Autonomic Blocking Agents in Patients With Hypertension. II. Hemodynamic, Ballistocardiographic and Electrocardiographic Effects of Hexamethonium and Pentamethonium, Circulation **8**:352, 1953.
5. Wilkins, R. W., and Judson, W. E.: The Use of Rauwolfia Serpentina in Hypertensive Patients, New England J. Med. **248**:48, 1953.
6. Wilkins, R. W.: Rauwolfia in the Treatment of Essential Hypertension, Am. J. Med. **17**:703, 1954.
7. Grob, D., and Harvey, A. M.: Observations on the Effects of the Autonomic Blocking Agent, Bis-trimethylammonium Pentane Dibromide (C_5) in Normal Subjects and in Patients With Peripheral Vascular Disease and Hypertension, and Comparison With Tetraethylammonium Chloride, Bull. Johns Hopkins Hosp. **87**:616, 1950.
8. Smirk, F. H., and Alstad, K. S.: Treatment of Arterial Hypertension by Penta- and Hexamethonium Salts, Brit. M. J. **1**:1217, 1951.
9. Smirk, F. H.: Blood Pressure Reduction in Arterial Hypertension by Hexamethonium and Pentapyrrolidinium Salts, Am. J. Med. **17**:839, 1954.
10. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension With Hexamethonium, Circulation **5**:20, 1952.
11. Freis, E. D., Partenope, E. A., Lilienfield, L. S., and Rose, J. C.: A Clinical Appraisal of Pentapyrrolidinium (M. & B. 2050) in Hypertensive Patients, Circulation **9**:540, 1954.
12. Freis, E. D.: The Discrepancy Between Home and Office Recordings of Blood Pressure in Patients Under Treatment With Pentapyrrolidinium. Importance of Home Recordings in Adjusting Dosages, M. Ann. District of Columbia **23**:1, 1954.
13. Schroeder, H. A.: Control of Hypertension by Hexamethonium and 1-Hydrazinophthalazine, Arch. Int. Med. **89**:523, 1952.
14. Smirk, F. H.: Practical Details of the Treatment of Hypertension by Hexamethonium Salts and by Pentamethylene 1:5-bis-N-(N-Methyl-pyrrolidinium) Bitartrate (M. & B. 2050A), New Zealand M. J. **52**:1, 1953.
15. Morrow, J. D., Schroeder, H. A., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. II. Toxic Reactions and Side Effects, Circulation **8**:829, 1953.
16. Wilkinson, E. L., Backman, H., and Hecht, H. H.: Cardiovascular and Renal Adjustments to a Hypotensive Agent (1-Hydrazinophthalazine), J. Clin. Invest. **31**:872, 1952.
17. Stunkard, A., Wertheimer, L., and Redisch, W.: Studies on Hydralazine: Evidence for a Peripheral Site of Action, J. Clin. Invest. **33**:1047, 1954.
18. Schroeder, H. A.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation **5**:28, 1952.

19. Assali, N. S., Kaplan, S., Oighenstein, S., and Suyemoto, R.: Hemodynamic Effects of 1-Hydrazinophthalazine (Apresoline) in Human Pregnancy: Results of Intravenous Administration, J. Clin. Invest. **32**:922, 1953.
20. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Rheumatic and Febrile Syndrome During Prolonged Hydralazine Treatment, J.A.M.A. **154**:23, 1954.
21. Perry, H. M., Jr., and Schroeder, H. A.: Syndrome Simulating Collagen Disease Caused by Hydralazine (Apresoline), J.A.M.A. **154**:670, 1954.
22. Feder, I. A.: Febrile Syndrome During Prolonged Hydralazine Treatment for Hypertension, New England J. Med. **251**:273, 1954.
23. Reinhardt, D. J., and Waldron, J. M.: Lupus Erythematosus-like Syndrome Complicating Hydralazine (Apresoline) Therapy, J.A.M.A. **155**:1491, 1954.
24. Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome Simulating Acute Disseminated Lupus Erythematosus. Appearance After Hydralazine (Apresoline) Therapy, J.A.M.A. **155**:1492, 1954.
25. Grob, D., and McKusick, V. A.: Effect of Hydrazinophthalazine and Hexamethonium on Renal Blood Flow and Function in Patients With Hypertension. (To be published.)
26. Kistner, R. W.: Treatment of the Acute Toxaemias of Pregnancy With Hypotensive Drugs, J. Obst. & Gynaec. Brit. Emp. **61**:463, 1954.
27. Meilman, E., and Krayer, O.: Clinical Studies on Veratrum Alkaloids. I. The Action of Protoveratrine in Hypertension, Circulation **1**:204, 1950.
28. Wilkins, R. W.: Veratrum Viride in Hypertensive Cardiovascular Disease, Mod. Concepts Cardiovas. Dis. **20**:89, 1951.
29. Hatch, F. T., Wertheim, A. R., Eurman, G. H., Watkin, D. M., Froeb, H. F., and Epstein, H. A.: Alterations in Sodium Chloride Protein and Fat Intake, Am. J. Med. **17**:499, 1954.
30. Gill, R. J., and Duncan, G. G.: Arterial Hypertension: The Therapeutic Effect of Cation Exchange Resins, New England J. Med. **247**:271, 1952.
31. Smithwick, R. H.: Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates, J.A.M.A. **147**:1611, 1951.
32. Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J., and Crumpton, C. W.: Effects of 1-Hydrazinophthalazine on Cerebral Hemodynamics and Oxygen Metabolism in Hypertensive Subjects, J. Pharmacol. & Exper. Therap. **103**:345, 1951.
33. Kelly, R. T., Freis, E. D., and Higgins, T. F.: The Effects of Hexamethonium on Certain Manifestations of Congestive Heart Failure, Circulation **7**:169, 1953.
34. Meilman, E.: Clinical Studies on Veratrum Alkaloids. III. The Effect of Protoveratrine on Renal Function in Man, J. Clin. Invest. **32**:80, 1953.
35. Bradley, S. E., and Bradley, G. P.: Renal Function During Chronic Anemia in Man, Blood **2**:192, 1947.
36. Nathanson, M. H., and Miller, H.: Clinical Observations on a New Epinephrine-like Compound, Methoxamine, Am. J. M. Sc. **223**:270, 1952.

VOL. 1 195

THE MANAGEMENT OF ESSENTIAL HYPERTENSION

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OL.
1
955

INTRODUCTION

I BELIEVE that we may be at the beginning of a new era with respect to the medical management of primary essential hypertension. If this is true it is largely because of two recent fundamental changes. The first and more obvious is the development of orally effective drugs for lowering blood pressure over long periods of time. The second and perhaps more important is the change in our attitude about the nature of this disease. This change in attitude has taken place gradually over the last ten years, following a period of disillusionment with the high hopes produced by Goldblatt's work suggesting that all hypertension may be "renal" in origin. The present concept of the pathogenesis of hypertension readily admits the important role of the kidney, but also includes the frequent roles of other organs and systems, such as the glands of internal secretion especially the adrenal, the central and autonomic nervous systems, and hereditary or familial tendencies such as hyperreactivity of the blood pressure to hypertensive stimuli and hypersensitivity of blood vessels to atherosclerotic and degenerative processes.

The several possibly pathogenic factors in hypertension have been aptly described as a mosaic which may vary in pattern from patient to patient but which should be considered by the physician in his appraisal of any single case. The consequences of this concept of hypertensive disease do not end at the way in which the physician thinks about the disease or even with how he studies a case, but also should influence what he does about it. First, of course, he must make a complete examination both in his office and in the laboratory of the hypertensive manifestations in the given patient. He must then try to modify the several abnormal or aggravating factors in the case in the hope of restoring a more normal physiology. In this attempt he may take a more or less urgent attitude depending upon the urgency of the case at hand. I like to compare this situation with that in the management of a patient with peptic ulcer in whom a similar mosaic of factors may be contributing to the patient's disease, requiring the astute physician not only to assess them but also to treat them by diets, drugs, psychotherapy, regulation of habits, or even by surgery. Similarly with the hypertensive patient the physician must be prepared to consider the use of

dietotherapy, psychotherapy, drug therapy, surgery, regulation of daily habits, or a combination of these measures. I do not regard such an approach as "doing everything because one does not know the right thing to do." Rather I regard it as multiform therapy for a multiform disease.

ATTITUDE OF THE PHYSICIAN TOWARD THERAPY

As indicated in the previous paragraph, the attitude of the physician toward therapy in hypertension is of great practical importance. Again and again we have seen a striking, not to say a miraculous, change take place in the patient's clinical condition when he came under the care of a physician who was aggressive in his treatment of the disease as contrasted with that of a previous physician who might have been nihilistic or at best timorous in his approach. Such experiences have re-enforced our own determination not to accept defeat in the therapy of any patient with hypertension without at least a vigorous trial of every suitable method of treatment in his case. It is also interesting that since we have developed this attitude there has been a striking shift in our own emphasis upon what we regard as the "unusual" in hypertensive disease, worthy of discussion with a colleague. Several years ago this was a patient who had responded brilliantly to drug therapy. We have ceased to regard this type of case as remarkable or as meriting more than passing comment. Instead we now concentrate on the occasional patients who do *not* respond to therapy, and we spend a great deal of time and effort in trying to solve the reason for our failure. This change in emphasis points up two obvious facts: One, that we are much more successful than we used to be in treating even severe or malignant cases of hypertension; but two, that we are not successful as yet in *every* case. Neither of these facts should be forgotten.

SELECTION OF CASES FOR TREATMENT

In my discussion I shall emphasize the management of the ordinary, ambulatory, hypertensive patient. I do this for two reasons: (1) This is by far the most common type of hypertensive case seen in the office practice of most physicians, and (2) other contributors to this symposium undoubtedly will emphasize the treatment of the more malignant cases. However, by such a selection I would not wish to imply that the treatment of malignant hypertension is not a useful and highly rewarding procedure, even though it concerns at most 1 or 2 per cent of my patients. Nothing can be more dramatic than the improvement that takes place in such patients on successful medical therapy. On the other hand, I do wish to imply that I believe it is very unwise to limit therapy to such malignant cases. I am convinced that no longer should we allow the earlier and milder cases to go untreated until they develop all the signs and symptoms of hypertensive vascular disease.

I believe the time has come when serious thought should be given to both the symptomatic and the *preventive* aspects of hypotensive therapy. This point of view does not overlook the fact that no convincing statistics are as yet available on whether the therapeutic methods now in use actually prolong

life expectancy. However, it finds support in the accumulating evidence that present methods do improve symptoms and lessen the severe complications of the disease. One might compare this empirical approach to therapy of hypertension with that regarding the use of digitalis in congestive failure, in which the drug is used more to improve the lot of the patient with organic heart disease than merely to prolong his life.

In the selection of cases for treatment one must rely on not one but numerous examinations of the patient along with an adequate history and a full laboratory appraisal of cerebral, cardiac, and renal functions. In the less malignant cases there is usually ample time to collect this type of information as a sort of "moving picture," which permits an accurate appraisal of the course of the disease, and furnishes an adequate background for evaluating the results of therapy. Finally, several examinations allow time for the establishment of rapport between the patient and the physician, who on the basis of a friendly acquaintance with the patient can learn of psychogenic factors, family difficulties, and other types of emotional trauma that may be playing a role in the patient's disease.

In taking a history the physician should stress the following: (1) evidences of a familial tendency toward hypertension, (2) a past history of extraordinary lability or intermittent elevation of the blood pressure, even when this has been of short duration (i.e., during pregnancy), (3) symptoms and signs of any type of renal disease, (4) neuropsychiatric stress such as family difficulties, business reverses, and the like, (5) specific symptoms suggesting hypertension including excessive fatigability, headaches, dizziness, tense feelings in the abdomen, shortness of breath, frequency or nocturia, blurring of vision, failing memory, and symptoms and signs of minor or major cerebral accidents.

In doing the physical examination the physician should particularly observe and record: (1) the appearance of the eyegrounds, (2) the state of the peripheral arteries and veins, (3) the size, thrust, rate, vigor, and sounds of the heart, (4) the state of the lungs, especially as to râles and vital capacity, (5) the signs of congestive failure (enlargement of liver and spleen, edema, ascites), (6) abnormalities of the kidneys and adjacent structures, (7) neurological abnormalities. In the laboratory he should pay special attention to the nonprotein nitrogen, or blood urea nitrogen, to phenolsulfonphthalein excretion (fractional), urinalysis; to blood hematocrit, hemoglobin, and red cell counts; to electrocardiogram; and to x-ray evidence relative to heart, lungs, and kidneys.

Factors which increase the gravity of hypertension in any given patient are: (1) male sex, (2) positive family history for hypertension, (3) early age at onset, (4) severe retinopathy, (5) renal functional impairment as denoted by proteinuria, subnormal excretory capacity, and other abnormalities, (6) extraordinary severity of or sensitivity to emotional trauma and stress, (7) cardiac strain and insufficiency, (8) evidences of cerebral impairment or stroke, (9) obesity, (10) family history of early atherosclerosis, (11) high diastolic pressure (over 140), and last, but most important of all, (12) a rapid progression of the signs and symptoms of severe hypertensive vascular disease.

As already mentioned, these various diagnostic and prognostic signs are of value not only in assessing the efficacy of treatment but also in gauging its ur-

gency. For example, if a young man of 28 with a strongly positive family history appears with a blood pressure of 230/140, Grade III eyegrounds, proteinuria, decreased phenolsulfonphthalein excretion, cardiac enlargement, and symptoms of paroxysmal dyspnea, the urgency for treatment is immeasurably greater than if the patient is a woman of the same age but without severe retinopathy, or renal and cardiac impairment. On the other hand, if the patient is a young woman with a strong family history, marked lability of the blood pressure, tachycardia, marked psychogenic factors in the background, and numerous symptoms but few organic signs of hypertension, the possibility of successful treatment with milder drugs may be considerably greater than in the first example given. In the first case one would "push" medical therapy in order to save the patient's life; in the latter case he would push therapy in order to make the patient's life more serene and comfortable and in addition in the hope that by lowering the blood pressure he would increase her life expectancy, if only by adding on years at the end of what would probably be a fairly full life-span without such therapy. Between these two extremes every conceivable combination of prognostic factors will be found with corresponding degrees of urgency, but in the final analysis, only the personal physician who knows the patient best can judge on the basis of his own experience and reading whether a given type of therapy is worth trying in that case. I know of no way in which to prove whether a given therapy will be worth while in a given case other than trying it. I therefore recommend that physicians who doubt the efficacy of modern drug therapy should at least use it before condemning it.

VOL 1 195

STEPS IN THE SELECTION OF DRUGS

If, as I mentioned at the outset, we are at the beginning of a new therapeutic era, it is at best the "early sulfonamide era" of chemotherapy for hypertension. We hope that some day, happily, we will have a "penicillin" in this field. Until that time we must do the best we can with the agents available. The list of effective drugs is steadily growing and there is every reason to hope that more effective new ones will be forthcoming soon. A knowledge of the nature and actions, as well as the side effects, of each of the several useful agents is absolutely necessary to their successful employment in hypertensive patients. Fortunately they can be arranged in order of their increasing side effects and toxicity and I believe that it is wise to try them in that order, beginning with the mildest, and ascending to the severest, but only if this is proved to be necessary in order to manage the blood pressure. We have referred to this process of ascending from the mildest to the severest agents as "going up the steps" (Fig. 1). This has been a useful concept because it also implies that one should "come down the steps" as soon as possible. How this may be achieved will be explained later.

The prototypes of the four kinds of agents of use in the medicinal therapy of hypertension are: (1) Rauwolfia, (2) veratrum, (3) hydralazine, (4) hexamethonium (going from mildest to severest). It is in that order that we "go up the steps."

Rauwolfia and its derivatives (alseroxylon, reserpine, and rescinnamine) are the mildest of the agents of clinical use for the treatment of hypertension.

Unique as hypotensive agents, they have a sedative-like or tranquilizing effect for which the average irritable hypertensive patient is extremely grateful. However, Rauwolfia derivatives also have a definite although moderate blood pressure-lowering action and a specific pulse rate-slowing effect. Indeed it was these two actions that brought the Rauwolfia derivatives into the field of hypertension from that of psychiatry. The side effects of these agents are mild unless large overdoses are used. These consist of nasal congestion, some increase in bowel motility, a tendency to gain weight, decrease in libido in men, and, with overdoses, vivid dreams or nightmares, or marked depression often associated with anxiety or agitation.

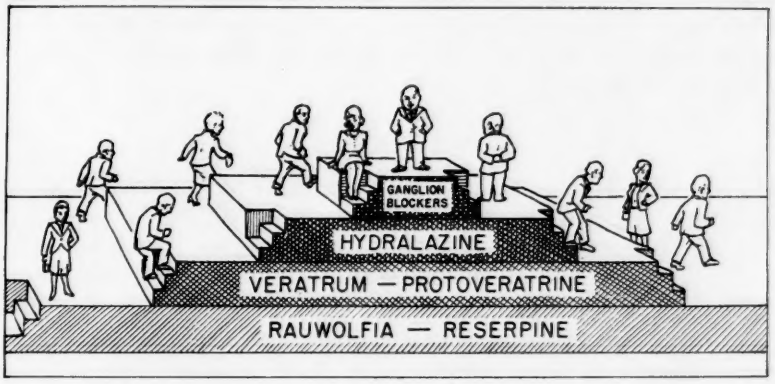

Fig. 1.—The steps in the drug treatment of essential hypertension.

Rauwolfia is most useful in relieving the symptoms of hypertensive patients such as headache, nervousness, dizziness, palpitation, and insomnia. Its actions, especially those on the blood pressure, are slow to appear, requiring some three to seven days, and are even slower to reach maximal effect, requiring some three to six weeks. Alone Rauwolfia is best in the mild labile hypertensive patient with anxiety neurosis and the symptoms ordinarily attributed to that state. But the best use of the drug is as a background or adjunctive agent when stronger blood pressure-lowering drugs must be employed. In this situation it markedly decreases the side effects of the other drugs or at least the patient's sensitivity to them, and in addition has a definite potentiating effect on their blood pressure-lowering action. Rauwolfia also has certain beneficial counteracting effects to some of the untoward side reactions of other drugs. For example, its bowel-stimulating action tends to offset some of the obstipation of hexamethonium, its pulse rate-slowing effect offsets the tachycardia produced by hydralazine, and its nausea-allaying effect decreases some of the objectionable emetic qualities of veratrum.

For these various reasons I prescribe Rauwolfia as the *first step* in all patients in whom I wish to try medicinal treatment for hypertension. The drug is given either in the form of the whole crude root, dose 100 mg.; the alseroxylon fraction, dose 2 mg.; or as reserpine, dose 0.1 mg., one to four times a day. Some workers

advocate starting this medication in larger doses on a four-dose schedule and then reducing the number of doses per day after one or two weeks when the effects of the drug begin to manifest themselves. In my experience it is preferable not to overdose with this drug, since it has a very flat dose-response curve in its hypotensive action, that is to say, it produces relatively small increments in hypotensive effect as its dosage is increased (above those suggested previously), whereas it does cause definitely more side effects.

Rauwolfia is continued for at least three weeks in patients in whom it is being tried alone (mainly those of milder, more labile type) before its effectiveness is judged. If there is any appreciable beneficial action, the drug is continued for at least another three weeks before further therapy is added to the schedule. Merely persisting in the use of this agent over a period of several months frequently suffices in bringing the blood pressure and the symptoms adequately under control.

VOL. 1 1955

"GOING UP THE STEPS"

The *second step*, when Rauwolfia alone seems not to have produced the desired hypotensive and clinically beneficial effects, depends somewhat on the patient's initial response to Rauwolfia. If the blood pressure has not responded at all or only very slightly while the pulse rate has come below 80 (preferably below 70), we may add hydralazine to the schedule. This is because hydralazine is one of the most effective hypotensive drugs now available in such resistant patients. However, if there has been some, but insufficient, lowering of blood pressure and pulse rate, we usually add veratrum as the second step.

Veratrum is a neurogenic vasodilator and vagal stimulant, and is emetic in doses uncomfortably close to the hypotensive ones. It is, however, not a toxic or dangerous agent. Veratrum is considerably more effective in conjunction with Rauwolfia than alone because then its hypotensive action is greater, while its emetic action is less. It is administered by mouth in the form of alkavervir in a dosage of 1.5 to 3 mg., or as protoveratrine in a dosage of 0.25 to 0.5 mg., four times a day. These dosages may be raised slightly as tolerated by the patient. The limit of tolerance is usually that dose which causes nausea and vomiting. Veratrum is particularly useful in slowing the pulse rate, if this effect has not been achieved on Rauwolfia alone, when the necessity of using hydralazine seems likely.

Hydralazine is a synthetic chemical which has the unique property of causing renal vasodilatation as well as generalized peripheral vasodilatation. It has some peripheral adrenergic blocking effects and, on acute administration, these may cause postural hypotension in some patients. However, these actions are not important on chronic oral dosage. Unfortunately hydralazine has some other very undesirable side effects and is potentially a toxic drug. Notable among its undesirable effects are the almost uniform production of tachycardia and palpitation when first administered and the production of angina pectoris in patients with coronary disease. It also frequently produces occipital headache, but this usually disappears on chronic usage.

Hydralazine's most "toxic" effect on chronic administration is the occasional production of a lupuslike, collagen disease associated with arthritis or arthralgia, dermatitis, fever, abnormal renal and liver functions, and the appearance of L.E. cells in the peripheral blood. Any suggestion of this syndrome is adequate indication for omitting the drug altogether. The phenomenon is somewhat "dose-connected" in that it almost never occurs on a dosage less than 200 mg. a day, and it almost never appears before several months of such sizable dosage.

When hydralazine is selected as the second step in treatment, the dosage is begun at a low level, i.e., 10 to 25 mg. four times a day and raised gradually until a hypotensive effect is achieved. Such a gradual institution of hydralazine lessens considerably the unpleasant side effects of headache and palpitation, especially when it is added to a background of Rauwolfia. For this reason we never prescribe hydralazine except in conjunction with Rauwolfia, and then only in a gradually increasing dose.

The *third step* is the addition either of veratrum or of hydralazine, whichever drug had not been used as the second step. It should be emphasized that at this step all three drugs are used *together*, namely Rauwolfia, veratrum, and hydralazine, and that their dosage is pushed until either untoward side effects or a desirable hypotensive action appears. This combination is definitely more effective than any combination of two drugs and usually is well tolerated on chronic dosage.

Hexamethonium, pentapyrrolidinium, and other ganglionic-blocking drugs are used as the *fourth step* in treating hypertension of the ordinary "benign" types only when a trial regimen of the other three drugs in combination has failed. (In malignant hypertension, however, blocking drugs may be used early because of the greater necessity of lowering the blood pressure immediately.) There is no question that the ganglionic blockers are among the most potent of the hypotensive drugs, particularly when their postural hypotensive effect is made use of. However, since these agents block all autonomic responses they produce many untoward side effects, including dryness of the mouth and throat, lack of visual accommodation, constipation or even obstipation, difficulty in micturition, impotency in males, lack of sweating, and, of course, marked postural hypotension, even to the point of collapse of the circulation.

The dosage of all ganglionic-blocking drugs is extremely critical and must be carefully "titrated," by which it is meant that the drug is started in small doses which are gradually increased until a clinical effect is achieved. For oral usage, hexamethonium is usually started in a dose of 31.25 mg., while pentapyrrolidinium is started in the dose of 10 to 25 mg., observing the blood pressure in the upright and horizontal positions frequently over the next two hours. If the initial dose produces no hypotensive action in the upright position, it is doubled four hours later, and the same observations are repeated in order to "titrate" the proper dose of the drug. Because of the extreme variability in the dosages that may be effective in different individuals and even in the same individual at different times, and because of the rapid development of tolerance, the titration and the regulation of dosage of blocking agents is extremely difficult and time-consuming.

Obviously the troublesome dosage characteristics of blocking agents should be weighed against the urgency for treating the blood pressure with them as judged from the total clinical and laboratory evaluation of the patient. If the course has been nonprogressive, there is considerably less urgency to treat the patient with blocking drugs than if the course has been rapidly downhill. Before instituting ganglionic blockers in a chronic regimen, I always satisfy myself not only that the patient is in urgent need of immediate hypotensive effects but also that the other three steps have been carried as far as the tolerance of the patient will allow, and finally that the patient understands and can manage the other side effects of a blocking agent. Critical among these side effects is obstipation, which must be counteracted with Rauwolfia and laxatives, such as a mixture of one half mineral oil and one half milk of magnesia taken at bedtime.

Unless a patient is a doctor or a nurse or the relative of such a professional person he is usually not asked to take and record his blood pressures at home or to manage the dosage of his drugs. This is for two reasons: (1) I feel that the management of the blood pressure is the physician's responsibility and should not be placed on the shoulders of the patient or his family. (2) The gains that this routine might provide have not appeared to me to justify the anxiety and irregularity of the treatment which it causes most patients. However, patients can be impressed with the symptomatology of excessive hypotension, and should be warned against its appearance, and cautioned to sit down or lie down, and to decrease the dosage of the drug slightly when this occurs.

VOL. 1 1955

As for the relative effectiveness of the various orally active ganglionic-blocking drugs, namely, hexamethonium, pentapyrrolidinium, and SU-3088, there is no convincing evidence as yet that one of these is definitely superior to the others when given over long periods of time in a large group of hypertensive patients. It is true that one of the drugs may act after resistance to another has developed, and in some instances the use of a newer preparation, particularly pentapyrrolidinium, seems to be somewhat smoother and easier to manage than that of hexamethonium. However, most accounts claiming great superiority for one product over the others have disregarded the very real value of previous experience with a similar agent by the same investigator. One has the feeling that some of the advantages claimed for a new drug may actually be due to the increasing skill of the physician as he uses first one and then another of these agents.

About one-third of the patients whom I see require a ganglionic blocker at some time, but it should be noted here that I see patients only on referral from their own physicians, which means that I tend to get more serious cases than the average physician sees in his office. I do not believe that the average physician would need to treat more than 10 per cent of his hypertensive patients with a ganglionic-blocking drug. Certainly I am convinced that there is no need whatever to treat *every* patient who comes into the office with these agents and that in general it is wise to hold blocking drugs in abeyance until the other three agents have been tried in combination. If it is still necessary to lower the blood

pressure even at the cost of the unpleasant side effects of the ganglionic blockers, then one may proceed, "titrating" the dosage with caution.

"GOING DOWN THE STEPS"

Once a satisfactory regimen is found and the patient has been brought up to a maximum or optimal dosage of drugs, he is held on this routine for about three months. No change is made unless it is necessary, as it frequently is, to increase the dosage of one or the other of the drugs in the schedule in order to maintain the hypotensive effect. In three to six months it is usually found that the patient has become well adapted to the regimen and that one may then be able to reduce the dosage of some of the drugs or even eliminate them entirely. If hexamethonium or another ganglionic-blocking agent is being used I usually try to reduce its dosage first and, if possible, finally to omit it altogether because of its fairly unpredictable side effects. I also usually try to omit veratrum, especially in patients who have a nearly normal blood pressure, because in this situation it can often be omitted from the regimen without any rise of pressure. Meanwhile I always attempt to reduce if not omit altogether the doses of hydralazine. This is done in the hope of avoiding any long-term toxic effects of the "lupuslike" type.

In time it is frequently possible with Rauwolfia alone or in combination with one other drug to control the blood pressure at levels where it has been brought only by a combination of more agents. In about one-third of the cases it is finally possible to omit all medication except Rauwolfia or one of its derivatives, which in some instances can be effective in extremely small doses in maintaining the blood pressure at its new low level. This process of "stepping down" the medication has been carried out in most of our cases without a rise in pressure, and in spite of the fact that on initial treatment several drugs together were necessary.

I believe that this "going down the steps," when it can be accomplished successfully, is one of the most encouraging features of our regimen, because this denotes that it is easier to control blood pressure at a new low level than to bring it down to that level from a higher pressure. Obviously this suggests that there may be some fundamental change in the underlying disease process as a result of this type of drug therapy. Whatever it means, it is quite helpful economically and psychologically to reduce the dosage of drugs that a patient has to take every day over long periods of time. It is interesting in passing to note, however, that we have not been able to omit Rauwolfia altogether from a regimen where it has seemed to have a definitely beneficial effect. Therefore we are at present committed to an indefinite program of using this drug to maintain the pressures at their new low level. Fortunately Rauwolfia appears to be ideally suited to this purpose because of its relative freedom from side effects, chronic toxicity, tolerance, or addiction.

RECAPITULATION

Here, then, is what we do for the hypertensive patients whom we see on an ambulatory basis: We take them "up the steps" as far as is necessary, keep

them at that level for a period of three to six months, and then try to go as far "down the steps" as we find is practicable. Measurements of blood pressure constitute merely the simplest and easiest of the methods for estimating the correct dosage and the effectiveness of such therapy. More important are the evidences of vascular disease, especially in the eyegrounds on ophthalmoscopic examination, in the myocardium as indicated by the electrocardiogram or the roentgenogram, and in the kidneys as shown by proteinuria and renal excretory capacity. Improvement in hypertensive symptoms, while difficult to evaluate objectively, is among the most gratifying of the beneficial effects of this type of drug therapy. Patients may be almost lyrical about their improvement on an effective regimen. Improvement from symptoms of cardiac decompensation, especially in patients on the ganglionic-blocking drugs, may also be very striking. Most striking of all, of course, are the evidences of recovery from acute hypertensive encephalopathy, which when associated with unconsciousness or convulsions may be relieved in an almost miraculous fashion when effective hypotensive therapy is employed.

VOL. 1 195

The detailed results of our method have been published elsewhere and have been supported by the studies of numerous other clinical investigators, who are now almost unanimously agreed on the broad general principles of this type of medicinal therapy, which incidentally would indicate that headway is generally being made with the method. In this type of management we make no attempt to interfere seriously with the dietary or other habits of the patient except in terms of keeping the weight and strenuous physical exertion under moderate control. Severe salt restriction has not been effective in our hands as a method for controlling blood pressure over a long period of time.

A word as to sympathectomy, which is still the only proved method of prolonging the life expectancy of hypertensive patients when studied by statistical methods after a five-year period. There is no question that sympathectomy is being used less frequently as more effective drugs are introduced. However, in our own clinic the operation is still performed on patients who have been resistant either to the *idea* of taking drugs or to the action of the drugs themselves. On the other hand, it is my firm belief that sympathectomy ultimately will disappear except in conjunction with essentially exploratory operations around the renal-adrenal area when it is suspected that either a tumor or an abnormal "Goldblatt kidney" may be responsible for the hypertension. In this situation it is quite easy to perform a lumbodorsal sympathectomy when no renal or adrenal cause is found to explain the hypertension. We do not advocate total adrenalectomy for hypertension, not because it may not be effective in lowering the blood pressure but because the postoperative difficulties of regulating these patients have appeared to us not to be feasible economically or practically.

SUMMARY AND CONCLUSIONS

Our current medical management of the ordinary ambulatory hypertensive patient has relied almost completely on the use of the following drugs in sequence

and in combination: Rauwolfia, veratrum, hydralazine, and hexamethonium, if and as necessary to control the blood pressure at reasonably lower levels. This procedure has been called "going up the steps," which implies the desirability of coming back "down the steps" as far and as soon as possible. In our hands this has been a practical and rewarding procedure.

OL.
1
955

MANAGEMENT OF THE PATIENT WITH PRIMARY (ESSENTIAL) HYPERTENSION

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VOL
1
195

FOR many years most physicians considered primary hypertension refractory to treatment. The physician was hampered not only by the lack of specific therapeutic methods but also by the lack of reliable information about the natural evolution of the disease. In the absence of any agent or procedure which could be relied on to lower the elevated arterial pressure, he was forced to concentrate on the treatment of the patient rather than the disease. This emphasis has been reversed in the last decade. Progress has been made both in the development of effective methods for lowering the blood pressure and in the accumulation of more comprehensive and precise data on the natural history of the patient with untreated essential hypertension. The new techniques of therapy have made it easier to treat at least one aspect of the disease, the blood pressure level. It is a paradox that the facility with which the blood pressure can be lowered has often made it more difficult for the physician to decide with wisdom how to treat the patient.

The etiology of primary hypertension is unknown. The mechanisms of development of the complications are still the subject of dispute. While the mode of action of some forms of therapy (sympathectomy and ganglionic-blocking agents) is at least partially understood, that of others (sodium-restricted diets, hydralazine, Rauwolfia) remains largely a subject for speculation. Although much is becoming known of the natural history of the untreated disease,[1] limited data are available concerning the course of the disease when treated by any of the new methods. Techniques are available which will reduce the blood pressure of most if not all patients. There is evidence that these measures may modify favorably some other manifestations of the disease process in some stages of the disorder. There is no evidence yet that the same is true of *all* manifestations of the disease in *all* stages.

Even though a long list of procedures and drugs is now available for the treatment of primary hypertension, the ideal agent is not yet at hand. The

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response to each form of treatment is unpredictable and, unfortunately, each method so far developed carries with it hazards and inconveniences. The physician must try to balance two unknowns. He must compare the future course of his patient if untreated (on which he has only statistical information) and the future course of his patient if treated (a course which has not yet been adequately explored even statistically). If his guess suggests an advantage from treatment, he must then balance this assumed advantage against the regimentation, invalidism, and side effects which may result from active treatment itself. When this is done, he may decide that the best treatment is no treatment.

EVALUATION OF THE PATIENT

A. *Diagnosis.*—Since the etiology and mechanism of primary hypertension are unknown, its diagnosis rests in part on a process of exclusion, and in many instances is difficult to establish. This diagnostic uncertainty has added to the difficulty of evaluating the various treatments. Many reported series actually contain patients with hypertensive disease of various etiologies whose courses on therapy cannot be compared validly with what is known of the natural history of untreated primary hypertension.

Precise diagnosis is important in the choice of therapy for each patient since (a) the potential benefits from control of the blood pressure are not necessarily the same in different disease states, (b) the hazards of the different treatments may vary in the different disease states, and (c) some of the known causes of elevated blood pressure call for specific therapies which are not indicated in primary hypertension.

A few points in the diagnostic evaluation deserve emphasis. A history of recurrent pyelonephritis, obstructive renal tract disease, acute glomerulonephritis, or the nephrotic phase of chronic glomerulonephritis makes primary renal disease with secondary hypertension more likely than essential hypertension. Similarly, the occurrence of proteinuria before the development of hypertension is usually indicative of primary renal disease. Primary hypertension seldom becomes evident before the age of 15 or after the age of 50. Onset outside this age span demands a particularly careful investigation to exclude known causes of elevated blood pressure.

The physical examination may be helpful in eliminating coarctation of the aorta, arteriosclerotic (systolic) hypertension, and polycystic kidneys as causes of the hypertension. It may give the clue to a diagnosis of an underlying endocrinopathy. The height of the diastolic blood pressure has little diagnostic value in an individual patient.

Urinalysis may be helpful. A normal urine in a hypertensive individual is more frequent in patients with primary hypertension than in those whose hypertension is secondary to pyelonephritis or glomerulonephritis. Pyelography is helpful in revealing such entities as unilateral renal disease, polycystic kidneys, pyelonephritis, and obstructive urologic disorders. Tests for exclusion of pheochromocytomas are warranted in many patients considered to have primary hypertension before the latter diagnosis is established.

B. *Determination of the Phase.*—Once a diagnosis of primary hypertension has been established, it is necessary to determine, and at frequent intervals to redetermine, whether the elevated blood pressure is accompanied by any specific complications. Is the patient in the uncomplicated phase? If so, his future is unpredictable but the prognosis is reasonably good and the need for treatment certainly not pressing. Is he in the complicated phase? Do his brain, eyes, heart, or kidneys already show evidence of damage? The appearance of these signs may indicate a need for treatment. Does he have "malignant hypertension"? Here, the time available for choice and initiation of therapy is short.

In order to determine the phase of the disease, it is helpful to consider the relative height of the diastolic blood pressure, the velocity with which it has been increasing, its lability, and responsiveness to such agents as Amytal sodium, or the immersion of a hand in ice water. As the disease state increases in severity, levels will be higher, in general more fixed, and less likely to respond to sedation or external stimulation. However, the height and responsiveness of the blood pressure alone do not establish the existence of any phase.

An evaluation of the optic fundi is helpful. In early hypertensive disease these are usually normal. As the disease progresses sclerotic changes, hemorrhages, and exudates may appear, and in the accelerated phase papilledema will develop. Keith-Wagener-Barker[2] Grades III and IV are useful in evaluating the course of the disease. Optic fundi of Grades I and II are not similarly helpful because equivalent changes are found in normotensive individuals.

Cardiac involvement may be estimated by determination of symptomatology and heart size and by electrocardiography. Central nervous system changes may manifest themselves as intellectual or emotional disorders, or there may be peripheral sensory or motor signs indicating major cerebral vessel pathology. Routine spinal fluid examination has not been necessary in our clinic.

Estimation of renal impairment is important in patients with essential hypertension. Fortunately, the usual function tests are adequate for most purposes. Urinalysis and estimation of ability to concentrate, blood urea nitrogen, phenolsulfonphthalein excretion, and in a few instances creatinine or urea clearances permit a reasonable evaluation of renal involvement.

When the presence or absence of cardiac, renal, central nervous system, or retinal changes has been determined, the physician is in a better position to evaluate the prognosis of the patient, the indications for therapy, and the choice of therapeutic agents.

GENERAL PRINCIPLES OF TREATMENT

The nature of hypertensive vascular disease is unknown and it cannot yet be cured. What, then, are the goals of therapy? They are to prolong life, to postpone or prevent complications, and to preserve or increase the patient's physical and mental capacity, his comfort, and his peace of mind.

In the complicated phase with cardiac or early renal manifestations, there is evidence that lowering the blood pressure level is often associated with the accomplishment of one or more of these goals. In the complicated phase with

VOL
1
195

cerebral manifestations (other than acute encephalopathy) and in the uncomplicated phase there is no proof yet that controlling the blood pressure will help accomplish these goals. In such circumstances, the natural desire of the physician to control the hypertension if he can, and his optimism if he succeeds, must be tempered with an unwillingness to add any serious incumbrances to the patient's life for the sake of a purely speculative gain.

In the absence of an agent which specifically cures the disease, treatment today consists of one or more of the following measures: education of the patient, weight reduction of the obese, low-sodium diets, hypotensive drugs, surgery, and judicious neglect. The decision to treat or not to treat must be based on the patient, the patient's reaction to his disorder, the phase of the disease, and, last, on the beneficial potential of the therapeutic agent when weighed against its disadvantages. Unfortunately every available method of lowering blood pressure imposes important restrictions and risks on the patient who submits to it. The particular capacity of each to help and harm must be considered in relation to each patient's peculiar needs and weaknesses.

Education of the Patient.—Hypertensive vascular disease is a chronic and usually permanent illness. The patient's welfare and the manifestations of the disease itself are affected by his emotional response to it. He is subjected to a constant barrage of misinformation and of information subject to misinterpretation from his reading, his social contacts, and even his medical contacts. He must be taught enough about his disease so that he can adjust to it, free himself of unnecessary anxieties, and meet with some sophistication the comments and reports about the disease and its treatment. He must learn what he should fear and avoid but, more important, he must learn what he need not fear and need not avoid.

Low-sodium Diets.—The use of low-sodium diets (less than 200 mg. of sodium per day) received support with Kempner's[3] observations during the administration of a rice-fruit diet to patients with hypertension. Studies[4] at the Columbia University Research Service of the Goldwater Memorial Hospital, on a group of advanced hypertensives whose blood pressure had remained elevated during a control period of six weeks of hospitalization, confirmed most of Kempner's findings. These results are summarized in Table I. There was a decrease in basal diastolic pressure in 72 per cent of the series. In 40 per cent the resulting blood pressures were below 160/95 mm. Hg. There was also significant improvement in symptoms, optic fundi, electrocardiograms, and the signs of heart failure. Unfortunately, the use of the rice-fruit diet was impractical in our hands. Patients found it monotonous and difficult to maintain for long periods.

Subsequent studies[5] have demonstrated that the important principle in the dietary treatment of hypertension is sodium restriction. The amounts of protein and fat in the diet do not appear to influence blood pressure levels. Therefore, it is possible to prescribe a more liberal dietary regimen which retains the efficacy of the rice diet while providing better nutrition and a more attractive variety of foods. When this is accomplished, the regimen is still difficult for

patients to maintain and some will rebel against its prolonged use. Many can accept it. The usefulness of this form of treatment in some hypertensives has been established. Probably because of the difficulty of getting patients to accept the strict rice regimen, it is less widely used than it might be.

TABLE I. RESPONSE OF PATIENTS WITH HYPERTENSIVE DISEASE TO THE RICE DIET

	BLOOD PRESSURE	OPTIC FUNDI	HEART SIZE	ELECTRO-CARDIOGRAM	CARDIAC FAILURE
No. of patients	50	36	33	28	17
Improved	36	13	19	9	9
Unchanged	14	26	14	18	8
Worse	0	0	0	1	0

The use of a low-sodium diet is not without hazard. It can contribute to nutritional inadequacy. In the presence of the appropriate abnormalities (excessive sodium loss) or adjuvant treatments (sodium eliminators), it can contribute to the development of the low-salt syndrome. In the presence of renal failure, it may accentuate the uremic state.

Surgery.—Sympathectomy is now less commonly employed in the treatment of hypertension than it was a few years ago. However, knowledge of its effectiveness is more certain than it is with either diet or drug therapy. Several large series[6,7] of patients treated surgically have been reported. More important, the follow-up periods over which the results have been evaluated have been longer than has yet been possible after either low-sodium diets or hypotensive drugs. It has been established that sympathectomy can increase the lifespan of some patients treated in the early accelerated phase of essential hypertension. There is some evidence that patients in the "complicated phase" may also have years added to their lives. Sympathectomy, when effective, works without the need for daily routine observance of diet or drug administration.

Sympathectomy, however, has certain disadvantages. There are the operative risk, loss of time, and expense to be considered. In some patients persistent postoperative complications such as intercostal neuritis and postural hypotension may occur. Results are notoriously poor in patients with significant emotional instability. As with every other form of treatment, its success in lowering blood pressure is unpredictable. The other forms of treatment can be tried experimentally in each patient and be continued or discontinued when they are found to produce more benefit or more harm. The surgical approach does not provide this flexibility. Hence the decisions, whether to use it and when is the optimal moment, are difficult and seldom the subject of agreement among consultants, even when they approve of the treatment abstractly.

Drugs.—A wide variety of hypotensive drugs are now available and have reached clinical trial. The various groups of drugs differ markedly in their pharmacologic actions and therefore both in their values and in their disadvantages. However, they are all used primarily to lower blood pressure, not

as specific treatments for the underlying disease. Their use does not call for picking the best or most powerful antihypertensive agent, but rather calls for selecting the agent most appropriate to the problem at hand.

The ganglionic-blocking agents (hexamethonium and pentapyrollidinium) may be considered as basically the same form of treatment as sympathectomy. Reports[8,9] appearing currently suggest that they may share some or all of the ability of sympathectomy to affect the course of the disease in its advanced and renal stages. Compared to surgery the drugs have both advantages and disadvantages. The degree of postural hypotension can usually be regulated by variation of dosage, and the patient's response adjusted to the needs of the moment, although this may require almost daily titration. But while the surgeon can restrict his effects to the sympathetic nervous system, the drugs also block the parasympathetic pathways and a group of undesirable side effects results from this action. The emptying of any hollow organ can be impaired, occasionally disastrously. The attention required to prevent constipation, which may result in increased absorption and dangerous overdosage of orally administered drug, is taxing on doctor and patient alike. Even with such care, accidents sometimes occur. These may be fatal or may be crippling through furtherance of thrombosis. Pentapyrollidinium may be preferable to hexamethonium for oral administration because of a higher and more reliable degree of absorption and a slightly more prolonged duration of action, but its absorption is still variable and uncertain. Until a ganglionic-blocking agent becomes available which is dependably and almost completely absorbed, the hazards listed will characterize this group. These hazards are probably as great as those entailed by sympathectomy.

Hydralazine is also capable of lowering the blood pressure of many hypertensive patients. Its action is unrelated to that of the ganglionic-blocking agents. It appears to act independently of the nervous system.[10] This different site of action may help explain why one patient may respond better to hydralazine than to ganglionic blockers and another patient may respond better to the blockers than to hydralazine. It also helps explain the fact that a combination may work better than either agent alone in some instances. It makes hydralazine a logical drug to try in a patient who has had a sympathectomy without adequate control of blood pressure.

Only one-half to two-thirds of patients are likely to show a definite hypotensive response to this agent (Table II), and it is not possible to predict in which patient this will occur. In short-term studies the drug has been shown to increase renal blood flow (which, if it were maintained, would be an advantage) and also to increase cardiac output (which, in some circumstances, may be a decided disadvantage). It must be used with caution in the presence of coronary artery disease. Most patients show some side effects, at least temporarily, but it is necessary to stop treatment in less than one-fifth. Even the severe, late toxicity, which mimics rheumatoid arthritis or systemic lupus erythematosus, usually develops slowly and remits on withdrawal, so that it presents less of a hazard than the suddenly developing toxicities encountered with the ganglionic-blocking agents. When compared with the low-sodium diet,[16] hydralazine appears to

have lesser therapeutic potency. However, the drug regimen is much easier for both the doctor and the patient to manage.

TABLE II. RESULTS WITH LONG-TERM USE OF HYDRALAZINE

NO. OF PATIENTS	DURATION OF THERAPY (MO.)	BLOOD PRESSURE RESPONSE	AUTHOR AND REFERENCE
17	½ – 3½	3 good; 14 none	Johnson et al.[11]
50	1 – 40	35 ↓ ≥ 20 mm. Hg	Schroeder[12]
41	1 – 5	31 ↓ ≥ 20 mm. Hg	Riven et al.[13]
86	30	½ good response	Taylor et al.[14]
40	2 – 16 (av. 8)	42% to normal + 23% lowered	Johnson [15]

The alkaloids of *Rauwolfia* are the most widely administered hypotensive agents at the present time. Although their site of action is postulated to be the hypothalamus, there is no clear evidence of where or how they act or of how fast they are excreted. When administered alone they are generally considered to have a mild hypotensive action in about 50 per cent of patients. This response is more likely to occur in patients in the early labile form of the disease when conventional doses are employed. If higher doses are administered a greater number of patients, including more with advanced disease, will respond. Rauwolfia is believed by some to enhance the hypotensive effectiveness of other drugs when used in combination. It causes bradycardia, which may offset the tachycardia resulting from hydralazine administration. Rauwolfia is much praised for its "tranquilizing" effect. It is widely considered to have no serious toxicity.

In our hands toxicity has been encountered if these alkaloids are used in much larger doses than those generally recommended. This is particularly observed during the treatment of patients with cerebral damage from vascular disease. Mental confusion, depression, and coma have occurred. More commonly, patients show a decrease of energy, alertness, and appetite, which may be undesirable and even dangerous. In one instance a severe asthmatic reaction followed drug administration.

These reactions, however, have not been commonly encountered to date in patients with less severe disease treated with the generally recommended doses (up to 1 mg. of reserpine or 100 mg. of the crude root preparations per day). There is some evidence that the drug accumulates in the body and persists for a long time after its administration is stopped. It is, therefore, not safe to assume that a patient who tolerates the drug well for short periods may not eventually show some undesirable effects.

The "tranquilizing" effect, which has appeared so desirable in handling tense, compulsive, hypertensive patients, is a mixed blessing. The physician may not always be in a position to decide with wisdom what personality his patient should wear. The casual assumption that a patient who no longer shows his worries is a happier, more productive person and a better provider for

VOL. 1 1955

his family has not always proved justified. It has sometimes been found necessary, after many months of treatment, to let a patient become himself again. It is possible that undesirable mental changes may be more apparent in patients who have already suffered cerebral damage than in those who have not.

Veratrum.—In this clinic, the narrow range between the hypotensive dose and the emetic dose of veratrum has led to its abandonment for the long-term treatment of hypertension. It may have use parenterally for the rapid control of hypertensive encephalopathic crises.

At the present time the physician has available three popular types of pharmacologic agents, Rauwolfia, hydralazine, and ganglionic blockers, which may prove effective in lowering elevated arterial pressure and which may or may not be tolerated by the patient. With each of these, dosage and the time schedule of administration may prove critical in their effectiveness in lowering pressure and in the development of toxicity. It is common experience that combinations of drugs from two or more of the groups often allow control of hypertension at lower dosage. This decreases the likelihood of toxic manifestations from each agent. As a result, this form of therapy is becoming popular. This approach appears logical and sound, but it too entails risks. In any given patient it is difficult to establish with certainty the usefulness of any agent unless the response is marked. The variability of blood pressure and its responsiveness to suggestion and enthusiasm are well known. Each material must be tested experimentally in each patient. Many patients may needlessly receive expensive, potentially toxic drugs for long periods of time. The judicious use of placebos may help eliminate unnecessary medication. There is no need for combined therapy when the total response is due to one drug.

It is our principle, when possible, to try the milder and less toxic drugs first, moving on to the more potent ones if the former are found inadequate. Often Rauwolfia is tried initially. Its onset of action is slow, the full effect apparently requiring accumulation of the drug in the body. It may be necessary to wait four weeks or more if 1 mg. of reserpine is given daily. A quicker effect may be obtained if 2 to 4 mg. is given daily for two weeks and then the lower dose substituted. A more stable pressure may result if the drug is given in divided doses.

If the response to Rauwolfia is inadequate, hydralazine may be added to it. The optimal dosage of this drug is sought. A placebo is then substituted for the Rauwolfia to determine whether the hydralazine alone is as effective as the combination. A period of weeks may be necessary to reach a conclusion. While hydralazine is not completely eliminated for twelve to twenty-four hours,[17] it must be given at six-hour intervals if a uniform response is to be obtained. Dosage is started at 10 mg. and increased at intervals of not less than one day, 10-25-50-100-150-200 mg. if needed. Careful observation, particularly for cardiac symptomatology, is required.

If the combination of Rauwolfia and hydralazine has failed and the disease state is sufficiently pressing, a ganglionic blocker may be tried. The patient should be hospitalized. In our opinion, these drugs are too difficult to institute with safety on any commonly available ambulatory basis except with unusually intelligent and cooperative patients or with home attendants as capable and as

constantly available as those found in a good hospital. If the methonium compounds are started during administration of one or more of the other drugs, it is again necessary to establish whether continuation of these is serving any useful purpose.

TREATMENT OF THE UNCOMPLICATED PHASE

There is no evidence that the natural history of patients in the uncomplicated phase of primary (essential) hypertension has been modified by treatment with any of the techniques available. Because of the long duration of this period in the course of the disease (averaging close to fifteen years) and because of the wide unpredictable variability in course and duration which an individual patient may exhibit before he enters the complicated phase, it will be difficult to accumulate definitive evidence on this point. It is natural to hope that it may eventually be shown that control of the blood pressure in this phase will prevent progress into the complicated or accelerated phases and slow the development of arterio- or arteriolosclerosis. At present there is no evidence to support this hope. If a drug were available that reduced blood pressure to normal in a useful percentage of patients without detrimental side effects, expense, or the development of tolerance, its use in patients in the uncomplicated phase of essential hypertension would certainly be justified. No such agent is now at hand. We therefore recommend no treatment for patients of this type other than the educative measures described previously.

It is advisable to follow these patients. They must be told that they have hypertension and must be convinced of the need for periodic examinations in order that any progression or complication of the disease which might be controlled by therapy can be detected early. They must be able to give a factual history to another physician if subsequently seen by one. Considering the comparatively good prognosis of the uncomplicated phase, information can be given without causing undue alarm.

Patients in the uncomplicated phase may develop symptoms. In many instances, reassurance, minor adjustments in the patient's daily routine, and attention to his anxieties are all that are required. Headaches may present a more stubborn problem. Simple things should be tried first: elevation of the head of the bed, the usual analgesics, and mild sedation are often successful. If these fail, a trial of one of the Rauwolfia preparations, for at least one month, may prove successful, but it should be used with the understanding that the trial is an experiment, that the results are uncertain, and that the physician must be continually alert to the development of subtle emotional and intellectual changes which may not be beneficial and which may outweigh the advantages of a reduced blood pressure.

TREATMENT OF THE COMPLICATED PHASE

More active treatment may be indicated when patients enter the complicated phase. This transition may be suspected when one or more of the following signs appear: (1) progressively rising and decreasingly labile diastolic blood pressure; (2) definite eyeground changes (hemorrhages, exudates, papilledema);

VOL. 1 195

(3) cardiac involvement (increasing heart size, electrocardiographic changes, angina pectoris, or infarction); (4) central nervous system involvement (thrombosis, hemorrhages, progressive cerebral degeneration, encephalopathy); and (5) renal function changes (proteinuria, falling phenolsulfonphthalein excretion, rising blood urea nitrogen).

Cardiac Involvement.—Even asymptomatic cardiac involvement in a hypertensive patient probably justifies an attempt to control the blood pressure. Whether or not there may be local vascular complications of the disease affecting the myocardium, reduction of the work load is rational. Cardiac enlargement and altered electrocardiographic patterns have been observed to revert toward normal during periods of reduced pressure. Cardiac decompensation may at times be relieved without any other treatment. However, as in any other type of heart disease, digitalis and diuretics are employed as needed. Weight reduction of the obese individual is important. The low-salt diet is of particular usefulness since it is not only an effective treatment for edema but in addition may influence favorably the degree of hypertension. If circumstances are suitable, this regimen may be tried initially. If the sodium-restricted diet fails to relieve the hypertension, one or more of the drugs may be useful. Rauwolfia is usually tested first, but it is seldom sufficiently effective alone and it should not be continued if benefit is not evident. Hydralazine, in spite of the fact that it speeds the pulse and increases the cardiac output, may be added very slowly. If its use results in a lowered blood pressure it may prove advantageous. The bradycrotic action of Rauwolfia will often control the tachycardia caused by hydralazine, and so this combination may prove useful in cardiac patients. In resistant situations the ganglionic blockers may be employed, but a sudden pressure fall in the presence of coronary artery disease can be disastrous.

Central Nervous System Involvement.—This group of patients may be subdivided into those with acute hypertensive encephalopathy, those with cerebral vascular accidents, and those with progressive cerebral degeneration or patients with more than one of these disorders.

The diagnosis of *acute encephalopathy* may be difficult to make. The patient may complain of increasingly severe and frequent headaches. Diastolic pressure rises above the previously established base line. There may be lethargy, stupor, and finally coma. Convulsions frequently appear and may be sustained. Papilledema is usual. If such a syndrome occurs in the absence of localizing neurological changes and in the absence of signs of intracranial bleeding (confirmed by spinal tap), a diagnosis of an acute encephalopathic attack may be entertained. If a patient becomes stuporous or comatose while receiving Rauwolfia it should be discontinued. The drug alone has produced these symptoms, which may be misconstrued as manifestations of acute encephalopathy. If the mental state is due to Rauwolfia, improvement may occur within twelve hours of its discontinuation. Treatment of an encephalopathic crisis is an emergency matter. Control studies are not available which establish that use of the rapidly acting antihypertensive drugs is more effective than long-tried empirical agents such as repeated spinal taps, intravenous magnesium sulfate, and hypertonic

glucose. Nevertheless the use of the newer antihypertensive drugs is probably preferable, provided conditions for their controlled administration are available. This requires hospitalization or its equivalent in trained personnel and available equipment. The parenteral use of either the ganglionic-blocking agents or the veratrum alkaloids can usually lower the blood pressure and apparently relieve the symptoms promptly. Hexamethonium is preferred primarily because it appears easier to continue treatment over more prolonged periods with it than with veratrum. The drug is administered by intravenous or intramuscular injection in amounts and at a frequency which are controlled by almost constant checks of the blood pressure level. The initial dose of parenteral hexamethonium or pentapyrollidinium should be not more than 1 mg. because occasional patients in this situation are disconcertingly responsive. The speed of reaction is so rapid that the dose can be increased until an effective total is reached without too much loss of time.

Acute cerebrovascular accidents are treated as in normotensive patients. Abrupt changes in blood pressure are probably undesirable when hemorrhage or thrombosis is taking place. Unless there is an unusual rise in pressure, it does not seem a propitious time for the introduction of new hypotensive measures. If thrombosis develops in a patient whose pressure has been lowered by drugs, the pressure should probably be allowed to rise somewhat. There is no established correlation between the development of or the improvement from cerebrovascular accidents and the concomitant height of the arterial pressure.

The treatment of patients with healed cerebrovascular accidents is unsatisfactory and difficult to choose. Although theoretically reduction of blood pressure might slow the development of additional arteriosclerosis or lessen the chance of hemorrhage, reduction of blood pressure has not been shown to prevent the development of subsequent thromboses. It is theoretically possible that reduced pressures and blood flow might increase the chance of thromboses developing beyond already existing arteriosclerotic plaques. Some patients quickly demonstrate symptomatically that their cerebral function cannot tolerate very much reduction of blood pressure. It seems reasonable to decrease very high pressures but not to attempt to bring them to "normal" and always to make all changes gradually over a period of weeks or months. There is a strong temptation to attempt to lower the pressure in patients who are partially crippled, and it is important for the physician to determine whether the disadvantages of the available agents do not outweigh the questionable validity of this impulse. Patients with hemiplegia and those with progressive cerebral degeneration without discrete major vessel thromboses present similar problems. They are often, like aged individuals in general, intolerant of severe salt restriction. As a group they are more likely than other patients to show mental clouding, loss of energy and appetite, even stupor, from Rauwolfia. In these patients with central nervous system impairment, vomiting, resulting from the use of veratrum, may make nutrition and hydration impossible to maintain. Furthermore, the urinary retention and the constipation and ileus which result from ganglionic-blocking agents may be more distressing and harder to relieve than with other

patients. Symptomatic postural hypotension in a patient already dizzy from cerebral arteriosclerosis is a poor therapeutic accomplishment. These patients often have enough confusion and loss of memory so that they cannot be trusted to observe the precautions necessary for the safe administration of the methonium compounds. The concentration on the disease required by these regimens is particularly undesirable psychologically for such patients. For these reasons traditional conservative methods are often preferable.

Renal Involvement.—In some patients with essential hypertension the major area of organ failure occurs in the kidney with destruction of tissue and function. The change may be slowly progressive or it may be rapid. In the latter instance it has been termed the "accelerated phase" ("malignant" hypertension). From studies of the natural history of patients who develop renal involvement, the prognosis for life appears sufficiently grave to warrant extreme measures. In these patients, the potential benefit from therapy far outweighs the disadvantages of treatment.

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955

There is accumulating evidence to support the contention that some patients in the accelerated phase of essential hypertension have an improved prognosis when the pressure is controlled by present methods. Based on this evidence and on the theory that renal involvement may be the result of continued diastolic hypertension, there is some justification for applying the results of treatment of the accelerated phase to patients with slowly progressive renal impairment. Certainly, some patients show continued deterioration in spite of treatment and go on to death in uremia even though their blood pressures have been held near the normal range. Nevertheless it seems warranted to treat both types similarly, with the belief that in some the rate of the vascular and renal damage will be slowed. From a therapeutic viewpoint the difference in the two types rests in the time available for trial of the milder agents and the urgency to employ additional therapeutic weapons.

If there is ample time, the low-sodium diet is worth a trial. Four to six weeks may be necessary to establish its efficacy. While danger of the low-salt syndrome exists, with careful observation it can be controlled. If the diet produces an inadequate effect, drugs may be added to the regimen. If the patient's condition indicates that therapeutic time is short, the low-salt diet and drugs may be started simultaneously and the effect of each agent clarified later if improvement is achieved.

Fig. 1 shows results in a patient with "malignant hypertension" but without elevation of the blood urea nitrogen, who had a partial response to a low-salt diet and an excellent and sustained response to hydralazine plus Rauwolfia. This is an *unusual* result. With most patients in the "malignant phase" it would be necessary to add ganglionic-blocking agents. However, such a trial of the milder agents is worth while *if* the patient's health allows the time, since the four years that this patient has been treated have been easy ones, without the elaborate controls and hazards which accompany the use of methonium compounds. As stated previously, the ideal response of this patient is not universal in another sense. Some patients with a good fall of blood pressure nevertheless suffer progressive renal failure.

If progress of the disease is rapid or if the blood urea nitrogen is already elevated, the prognosis is poor under any form of treatment and delay in control adds to the risk. In such patients the ganglionic-blocking agents should be employed immediately with hydralazine and Rauwolfia added if necessary. If satisfactory control is achieved the ganglionic blocker may later be slowly and cautiously withdrawn while the hydralazine and Rauwolfia are continued, to see if the patient can be maintained on this simpler regimen. Such a maneuver can be attempted only under close and continued observation.

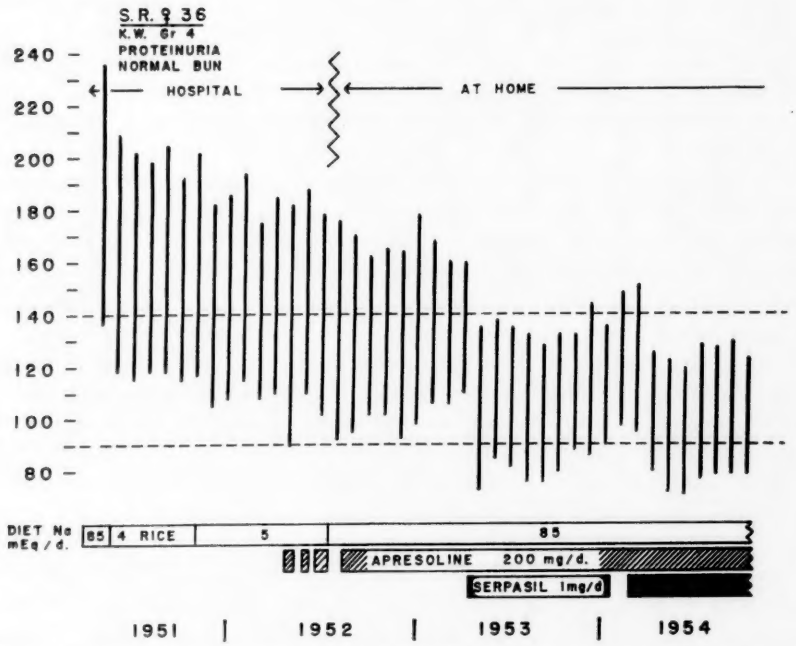

Fig. 1.—The course of blood pressure during four years' observation under various therapeutic regimens in a patient originally diagnosed as having essential hypertension in the accelerated phase. Each blood pressure line represents a monthly average of resting pressures. Optic fundi improved progressively during the first year. She has been on full activity for the past two years and has no detectable pathology.

Sympathectomy remains the most thoroughly proved form of treatment for patients in the early accelerated phase. If trial of diet and drug therapy fails to elicit a response and the patient has not developed significant nitrogen retention, surgery holds some hope and is worth recommending. It also warrants consideration for those patients who cannot or will not follow a medical program. Observance of the regimen for methonium therapy or for low-salt diets requires a good intelligence, patience, interest, and certain financial resources. Many patients lack one or more of these attributes, and under such circumstances sympathectomy may be found safer and more effective than its medical counterpart.

Uremia is handled no differently than it is in any other disease state. Sympathectomy is contraindicated. Hypotensive drugs may be tried in desperation, but results are at best questionable. It seems reasonable to seek a moderate reduction of extreme blood pressure elevations, but abrupt falls or returns to "normal" are avoided in hope of maintaining maximal renal blood flow. Salt restriction may prove rapidly disastrous and is contraindicated. There is not yet sufficient evidence available to allow evaluation of the safety of Rauwolfia in this state.

SUMMARY

The blood pressure of many patients with primary hypertension may be lowered by low-sodium diets, antihypertensive drugs, or sympathectomy. Some of these patients treated with such measures are benefited.

The physician must base and evaluate his treatment on an understanding of the natural history of primary hypertension in untreated patients. The possible benefits of treatment must be weighed against the disadvantages and dangers peculiar to each regimen in the various stages of the disease.

The choice of treatment represents an experiment in each patient. Neither the antihypertensive effect nor the disadvantageous effects of any treatment can be predicted with confidence before trial in the individual. The choice of which agent to try first is made principally on an evaluation of the rapidity of progression of the disease process and on the patient's ability and willingness to follow the necessary regimen. Emphasis is placed on avoiding, when possible, the more complex and hazardous forms of therapy until the simpler and less hazardous ones have been found inadequate.

Current experience permits certain generalizations:

1. No specific treatment other than education is recommended for the patient in the asymptomatic uncomplicated phase. Symptoms, in the absence of demonstrable organ involvement, are treated conservatively. The alkaloids of Rauwolfia are sometimes useful.

2. Progression of essential hypertension into the complicated phase implies the existence of atherosclerosis. All induced reductions in blood pressure in such patients carry the risk of significant local alterations in arterial blood supply. Changes are therefore made as slowly as possible.

3. In the complicated phase of essential hypertension, even asymptomatic cardiac enlargement or any degree of decompensation justifies an attempt to lower the blood pressure. The possible hazards of the various forms of treatment and of lowered pressure are a limiting factor.

4. Renal damage, without uremia, is considered an indication for antihypertensive therapy; the potential benefit far outweighs the disadvantages of treatment. The rate of progression of the disease determines the choice of therapeutic agents and the rapidity of pressure change desired.

5. Acute hypertensive encephalopathic crises call for immediate lowering of the blood pressure by parenterally administered methonium compounds, if the facilities for their controlled administration are available.

6. The value of prolonged antihypertensive therapy for most patients with cerebral damage has not been demonstrated.

It is now sometimes possible to help patients with hypertension. It is more possible than ever before to hurt them.

REFERENCES

1. Perera, G. A.: Hypertensive Vascular Disease; Description and Natural History, J. CHRON. DIS. **1**:33, 1955.
2. Keith, N. W., Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension. Their Course and Prognosis, Am. J. M. Sc. **197**:332, 1939.
3. Kempner, W.: Treatment of Kidney Disease and Hypertensive Vascular Disease With Rice Diet, North Carolina M. J. **5**:125, 273, 1944.
4. Watkin, D. M., Froeb, H. F., Hatch, F. T., and Gutman, A. B.: Effects of Diet in Essential Hypertension. II. Results With Unmodified Kempner Rice Diet in Fifty Hospitalized Patients, Am. J. Med. **9**:441, 1950.
5. Hatch, F. T., Wertheim, A. R., Eurman, G. H., Watkin, D. M., Froeb, H. F., and Epstein, H. A.: Effects of Diet in Essential Hypertension. III. Alterations in Sodium Chloride, Protein and Fat Intake, Am. J. Med. **17**:499, 1954.
6. Smithwick, R. H.: Hypertensive Cardiovascular Disease; Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates, J.A.M.A. **147**:1611, 1951.
7. Hammarström, S., and Bechgaard, P.: Prognosis in Arterial Hypertension, Comparison Between 251 Patients After Sympathectomy and Selected Series of 435 Non-operated Patients, Am. J. Med. **8**:53, 1950.
8. Schroeder, H. A., Morrow, J. D., and Perry, H. M., Jr.: Studies on the Control of Hypertension by Hyphex. I. Effects on Blood Pressure, Circulation **8**:672, 1953.
9. Smirk, F. H.: Practical Details of the Treatment of Hypertension by Hexamethonium Salts and by Pentamethylene 1:5-bis-N-(N-methyl-pyrrolidinium) Bitartrate (M&B 2050 A), New Zealand M. J. **52**:325, 1953.
10. Stunkard, A., Wertheimer, L., and Redisch, W.: Studies on Hydralazine; Evidence for a Peripheral Site of Action, J. Clin. Invest. **33**:1047, 1954.
11. Johnson, R. L., Fries, E. D., and Schnoper, H. W.: Clinical Evaluation of 1-Hydrazinophthalazine (C-5968) in Hypertension, With Special Reference to Alternating Treatment With Hexamethonium, Circulation **5**:833, 1952.
12. Schroeder, H. A.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation **5**:28, 1952.
13. Riven, S. S., Pocock, D. G., Kory, R. C., Roehm, D. C., Anderson, R. S., and Meneely, G. R.: The Control of Hypertension With 1-Hydrazinophthalazine (Apresoline), Am. J. Med. **14**:160, 1953.
14. Taylor, R. D., Corcoran, A. C., Dustan, H. P., and Page, I. H.: Further Evaluation of Hydralazine in Treatment of Hypertensive Disease, Arch. Int. Med. **93**:705, 1954.
15. Johnson, R. P.: The Treatment of Hypertension With 1-Hydrazinophthalazine (Apresoline), Am. Heart J. **46**:593, 1953.
16. Stunkard, A. J., Eurman, G. H., Wachspress, M., and Wertheim, A. R.: Treatment of Hypertensive Disease With Hydralazine: Comparison of Its Action With That of Low Sodium Diet in Hospitalized Patients, Am. J. Med. **17**:712, 1954.
17. Schulert, A. R.: Unpublished data.

VOL. 1 195

Book Reviews

CLINICAL CYTOLOGY USING THE MAY-GRÜNWALD-GIEMSA STAINED SMEAR. Two volumes. By P. Lopes Cardozo, M.D. Pp. 128 (text), pp. 192 (atlas), with 197 plates (74 in color). Leyden, The Netherlands, 1954, L. Stafleu. Price 72.50 Dutch Guilders.

This work, consisting of one volume of 128 pages of text and a second volume of illustrations (192 pages) with 197 plates, 74 in color, is an appropriate and valuable contribution in a field established by Virchow, developed by some hematologists as well as the pathologists, and exploited more recently by Papanicolaou. Clinicians, with the exception of hematologists, have neglected cytology. Papanicolaou's work has now demonstrated the great usefulness of the study of exfoliative cytology in clinical medicine, and the present work is designed to broaden the horizon and application of cytology still further. A clinician, Dr. Lopes Cardozo, presents his own experience in exfoliative and nonexfoliative cytology and demonstrates the ways in which this science can be employed in differential diagnosis.

The study is based on the use of smears, dry-fixed in air and stained by the panoptic May-Grünwald-Giemsa method. There is a concise discussion of the eighteen cytologic characteristics of tumor cells and the interrelationships between cytology and histology. In turn the author discusses the technique and application of these methods to the study of tumors and swellings of the neck, the puncture of the spleen, the lymph nodes and the thyroid, and their interpretation, the clinical cytology of the lung, the cytology of pleural and ascitic fluids, and the cytology of the prostate. The treatment is not exhaustive, and some topics already well covered in the literature are deliberately omitted. The material is presented concisely and clearly and the illustrations are all most useful. The translation is excellent, the production is artistic.

This important treatise should prove to be both a useful guide and an important stimulus to the further development of the field of diagnostic cytology.

Maxwell M. Wintrobe

PHARMACOLOGY IN MEDICINE. Edited by Victor A. Drill, Ph.D., M.D. Pp. 1264; indexed. New York, 1954, McGraw-Hill Book Company, Inc. Price $19.50.

For one person to attempt to review a textbook covering a major scientific area is only slightly less dangerous than for one person to write such a book. The publishers of this latest pharmacologic opus have avoided the latter error. They have enlisted the services of no less than eighty-one "experts," in and out of the field of academic pharmacology, to write chapters on a great variety of topics. The presence of forty-one full professors of pharmacology on the list of contributors is in itself quite an achievement.

The book has many excellent qualities. The use of multiple authors is to be commended, as is the use of nonpharmacologists to cover certain highly specialized areas. Many of the writers command (and deserve) respect as experts in the fields which they cover. In certain instances, it is hard to imagine anyone more capable of describing the material. Many chapters, accordingly, are well written, with length appropriate to content, and text that is essentially free from error.

Other aspects of the book are less satisfactory. At least one major topic (chemotherapy) is so subdivided (fourteen chapters) that the results seem less satisfactory than would have been the case if only a few "experts" had been involved. An occasional chapter is less than adequate. Some chapters seem completely unnecessary. Others are inordinately long and unnecessarily detailed (sixteen pages are devoted to lead). It is troublesome, in a book which boasts of "having

each subject presented by an expert," to find gross errors ("normal plasma HCO_3 concentration of 40 meq. per liter") or obvious lack of familiarity with key papers in the literature. The weight of the book and its size make it almost impossible to read except at a desk. The price will depress many a medical student. The attractive typography and layout are coupled with a strange method of pagination, which will cause at least temporary annoyance to many.

These criticisms are made more in sadness than in anger. So much of the book is good that it seems a pity not to have had a tighter hand on the editorial reins. Perhaps subsequent editions will eliminate some of the objections to the present volume. Despite its faults, the book must be recommended—at the moment—as the most satisfactory textbook of pharmacology on the market.

Louis Lasagna

VOL
1
195